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Review Article

Fluid therapy in ICU – A review

ABSTRACT

The most common indications of fluid resuscitation in critical care settings are severe hypovolemia, sepsis, trauma, burns, and perioperative fluid loss. Evaluation of intravascular volume status and the ability for identifying patients who might profit from volume expansion is vital. Traditional markers such as central venous pressure and pulmonary capillary wedge pressure have poor predictive value for fluid responsiveness. Dynamic indices such as pulse pressure variation, stroke volume variation, tidal volume challenge, and passive leg raise test are recommended to predict fluid responsiveness over static markers. The next perplexing part of fluid therapy is the choice of fluid resuscitation. The simplest answer is to provide crystalloids and avoid synthetic colloids (hydroxyethyl startch, gelatin, and dextran). Among the colloids, albumin has a role in certain clinical conditions in critical care settings. Between normal saline and buffered solutions, buffered solutions have the advantage of reducing acid–base disturbances, and chloride burden, and are likely to prevent renal failure. However, the advantage of buffered solutions did not consistently show up in large randomized controlled trials. Although administering fluids is a common therapeutic approach in critical care settings, administering fluids excessively has been linked to fatal outcomes. The resuscitation, optimization, stabilization, and evacuation concept describes the use of a dynamic fluid strategy to optimize benefits and prevent the negative effects of fluid overload. After receiving a patient in an emergency room or intensive care unit with hemodynamic instability, the first thing that comes to mind is whether or not the patient would benefit from fluid administration. How to predict fluid responsiveness? What type of fluids should be administered? When to stop administering fluids and start evacuation are vital questions confronted in day-to-day practice. In this article, we would like to discuss these issues and provide recommendations for current practices.

Keywords: Fluid responsiveness, phases of fluid administration, type of fluid

INTRODUCTION

Fluid administration is the first line of treatment for those presented with acute circulatory failure. Identifying patients who can benefit from fluid therapy is crucial because both inadequate and excessive resuscitation are associated with significant mortality and morbidity.[1] Fluid responsive markers can be categorized as static and dynamic and dynamic parameters are superior to static parameters.[2] The selection of fluid resuscitation is the next confusing aspect of fluid therapy. Undoubtedly, crystalloids are the most often utilized resuscitation fluids. With a few exceptions, the majority of studies indicate that IV fluids with a near physiological level of chloride are often the best initial fluid choice. There are numerous uncertainties around the prediction of fluid responsiveness, type of fluid, dose, timing of IV fluid administration and fluid evacuation. This review will make an effort to address these concerns.

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PREDICTION OF FLUID RESPONSIVENESS

The primary line of treatment for acute circulatory failure is the administration of fluids. The aim of fluid administration is to improve tissue perfusion and enhance oxygen delivery. According to various studies, only half of the individuals presenting with shock will respond to fluids.[3] Fluid administration is a double-edged sword. Both under and

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excess resuscitation are associated with substantial mortality and morbidity.[1]

The term fluid responsiveness is intended to be a marker of preload responsiveness. The definition of fluid responsiveness still varies but it is commonly defined as an increase in a parameter of cardiac function (stroke volume [SV]/cardiac output [CO]) by 10%–15% after an intravenous (IV) fluid bolus.[4] Fluid responsiveness can occur only if both ventricles work on the ascending, steep part of the Frank–Starling curve, i.e., in cases where CO is preload dependent.[5] Dynamic indices are proved to be superior to static cardiac filling pressures in predicting fluid responsiveness.[2] Approach to a patient with signs of hypo perfusion depicted in Figure 1.[6]

Static markers of preload

Central venous pressure

Pressure in the vena cava which can be used as an estimate of preload and right atrial pressure. Utilized as a rough approximation of right ventricular (RV) preload and, to a lesser extent, left ventricular (LV) preload. The pressure within superior vena cava (central venous pressure [CVP]) was measured relative to the atmospheric pressure. Transmural pressure at the end of expiration represents intravascular pressure whereas intrathoracic pressure is equivalent to atmospheric pressure. Hence, CVP should be measured at the end of expiration. Factors influencing transmural pressure (positive end expiratory pressure [PEEP], pleural effusion, cardiac tamponade, intra-abdominal hypertension, etc.). These conditions make it more difficult to interpret CVP. According to numerous studies, CVP is not a reliable indicator of fluid responsiveness.[7] However, extreme values have a role in resuscitation. Fluid response is highly likely in CVP values <6 mm of Hg and less likely in values >15 mm of Hg.[8]

Pulmonary capillary wedge pressure

Pulmonary capillary wedge pressure (PCWP) is a potentially useful index of LV filling pressure and pulmonary vascular congestion. Since there are no valves between pulmonary capillaries and left atrium, PCWP reflects left atrial pressure when the flow is obstructed by inflating the balloon. Similar to CVP, PCWP was shown in multiple studies to be an unreliable indicator of fluid responsiveness.[9] Due to its invasive nature and associated complications, it has fallen out of favor.

Dynamic variables

Current guidelines for the management of critical patients recommend the application of dynamic variables to evaluate fluid responsiveness. Considered dynamic because they are measured by monitoring changes in physiological responses based on heart - lung interaction. A rise in intrathoracic pressure during inspiration in a patient on a mechanical ventilator causes a decrease in venous return. If the patient is on a steeper part of the cardiac function curve, the decrease in venous return causes a reduction in SV. The magnitude of change in SV is represented by fluctuations of arterial blood pressure and plethysmographic wave patterns.

Pulse pressure variation

It is defined as the percentage of change in pulse pressure during one mechanical breath.

$$PPV = \frac{\text{pulse pressure max - pulse pressure min}}{\text{Pulse pressure mean}} \times 100$$

Pulse pressure variation (PPV) > 12% predicts fluid responsiveness with sensitivity of 88% and with a specificity of 89%.[10]

Stroke volume variation (SVV): Represents respiratory-induced variations in SV during a single mechanical breath.

$$SVV = \frac{\text{stroke volume max - stroke volume min}}{\text{stroke volume mean}} \times 100$$

SVV > 10%–12% predicts fluid responsiveness.[11] SVV is marginally less accurate than PPV because of computational limitations in the pulse contour analysis.[12] However, a PPV value that falls between 9% and 13%—is referred to as the "gray zone."[13]

Limitations:

1. Spontaneous breathing: Spontaneous breathing efforts, in contrast to positive pressure ventilation increase venous return rather than decrease it result in either negative or ambiguous findings
2. Low tidal volume ventilation: Fluid responsiveness can be most accurately predicted by dynamic markers at tidal volumes of 8 mL/kg. Low tidal volumes during lung-protective ventilation may not be adequate to induce changes in SV
3. Arrhythmias: Result in irregular cardiac filling which decreases the utility of dynamic markers
4. RV dysfunction: During a mechanical breath, the right ventricle's output further declines because the rise in afterload erroneously suggests greater fluid responsiveness.

Tidal volume challenge

It is proposed to improve the reliability of PPV during low tidal volume ventilation. After noting the PPV at 6 mL/kg, raise the tidal volume to 8 mL/kg for 1 min, and once again record the PPV then restore the tidal volume to 6 mL/kg. ΔPPV 6–8 >3.5% predicts fluid responsiveness with high accuracy.[14]

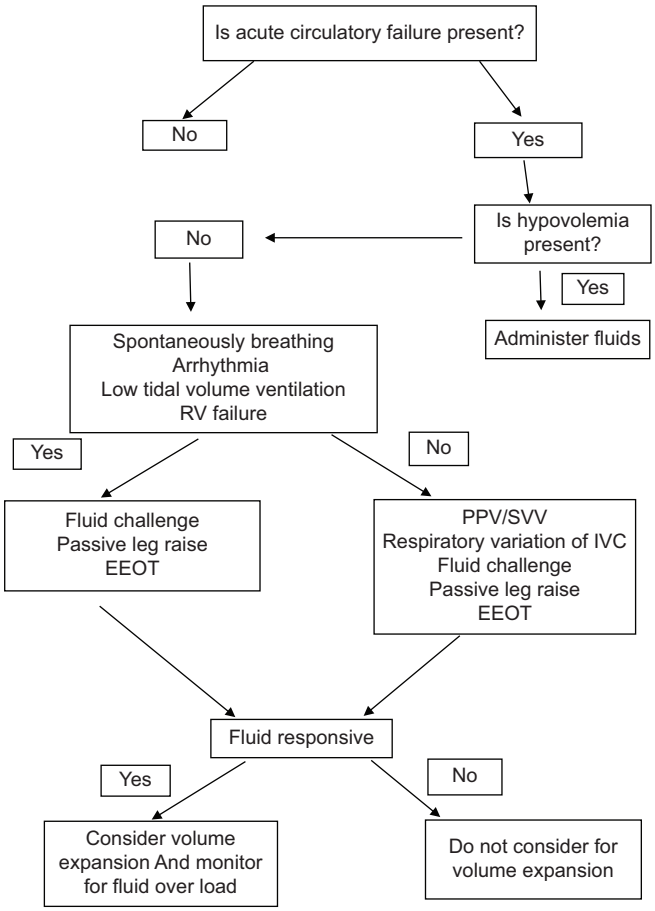

Figure 1: Approach to circulatory failure, Modified from Monnet *et al.* PPV: Pulse pressure variation, SVV: Stroke volume variation, EEOT: End expiratory occlusion test, IVC: Inferior vena cava

Fluid challenge

It consists of two main components. The first is the amount of fluid provided, while the second is the rate of fluid administration. The minimum amount of fluid that has to be administered to challenge the system is 4 mL/kg[15] and it is recommended that it should be given over a period of 5–10 min.[16] After the fluid challenge, a rise in CO/SV of more than 10% is interpreted positive.

Mini-fluid challenge: 100–150 ml of fluid should be given over 1–2 min. The threshold for the variation of CO after a mini-fluid challenge is small and it is 5% on average.[17]

Disadvantage with the fluid challenge is it requires real-time CO monitoring to assess the responsiveness. Alternatively, velocity time integral can be used to determine fluid responsiveness but which is an operator-dependent.

Passive leg raise test

It is a bedside maneuver. Transferring a patient from a semi-recumbent position to a position where the trunk is horizontal and the lower limbs are elevated at 30°–45° mobilizes blood from the splanchnic territory and the lower limbs. Which results in self-transfusion of roughly 300 mL of blood which is reversible.[18] A passive leg raise (PLR)-induced rise in CO of more than 10% is considered to predict fluid responsiveness with high accuracy.[19]

- Advantages: Reliable in patients with spontaneously breathing and with arrhythmias
- Disadvantages: Contraindicated in patients with intracranial hypertension, unstable pelvic fractures, and gives false-negative values in patients with intra-abdominal hypertension.

End expiratory occlusion test

A rise in intrathoracic pressure during inspiration in a patient on a mechanical ventilator causes a decrease in venous return and during expiration, there will be an increase in venous return. If the end-expiratory occlusion is prolonged sufficiently, the right-sided cardiac preload is transferred to the left side which increases CO.

Transiently interrupting mechanical ventilation at end-expiration for 15 s,[20] which results in a transient increase in preload and increase in CO or SV of <5% predicts fluid responsiveness.[21]

Limitations – Patients who are not on mechanical ventilator support and who cannot tolerate breath hold for 15 s end-expiratory occlusion test (EEOT) is not useful.

Peripheral perfusion index

It is a variable which is derived from pulse oximetry. The peripheral perfusion index (PPI) represents the ratio between the pulsatile and the nonpulsatile blood flow. It depends on the blood flow in the peripheral circulation and is an indirect marker of CO and vasomotor tone. A 9% increase in the PPI following a passive leg raising test[22] and 2.5% after an end-expiratory occlusion test[23] could predict fluid responsiveness with fair predictive value.

TYPE OF FLUID ADMINISTRATION – WHAT FLUIDS SHOULD BE GIVEN?

The 0.9% Na Cl fluid was historically the first fluid to be utilized. Later, Sydney Ringer and Alexis Hartman developed the physiological salt solution, which contains less chloride and other electrolytes, now termed as balanced/buffered solution. Following that, albumin and other synthetic colloids are used as resuscitation fluid.

At present, none of the commercially available solutions contain electrolyte and buffer concentrations comparable with those of plasma.

Normal saline: Normal saline (0.9% sodium chloride) is still frequently used despite concentrations of sodium and chloride (154 mmol/L) well above those found in plasma. Since the strong ion difference of normal saline is zero, large-volume administration leads to hyperchloremic acidosis. Chloride-rich solutions trigger tubuloglomerular feedback, which causes afferent arteriolar constriction, lowers glomerular filtration rate, and results in acute kidney injury (AKI).[24] However, these outcomes were not constant among randomized controlled trials.[25] Normal saline is preferred in patients with traumatic brain injury and with raised intracranial pressure due to its relative hypertonicity.

Buffered solutions: Buffered crystalloid use has increased due to concerns about potential side effects from regular saline's high chloride concentration. The two major anions found in extracellular fluid are bicarbonate and chloride. Hence, raising the bicarbonate level in the fluid composition will optimize the side effects of hyperchloremia.[26] However, bicarbonate-containing solutions are unstable in plastic containers. Instead, alternatively, metabolizable anions such as lactate, acetate, gluconate, and malate are utilized. These molecules act as buffers and provide bicarbonate. In individuals with severe liver impairment, RL is not the preferred fluid since lactate is metabolized in the liver and acetate uses an additional hepatic pathway to metabolize, acetate-based solutions are preferred. However, RL administration in patients with liver dysfunction is not an absolute contraindication.

Trials suggesting the superiority of balanced crystalloids

SMART TRIAL, (2018) SALT ED TRIAL (2018) – balanced crystalloids are better in terms of mortality and renal replacement therapy (RRT) sessions.

Trials did not show difference between normal saline and balanced crystalloids

SPLIT TRIAL (2015), SALT TRIAL (2017), BASICS (2021), PLUS (2022).

Nevertheless, to date, no study has shown that saline is superior to balanced crystalloids.

Balanced crystalloids are preferable in patients with metabolic acidosis, hyperchloremia, those at risk of renal injury, or with raised creatinine.

Normal saline is preferable in patients with metabolic alkalosis, hypochloremia, and cerebral edema.

Colloids

Colloid solutions contain large molecules that prolong the time the fluid remains in circulation. The benefit of colloidal solutions in fluid treatment is their ability to save volume and help in the prevention of volume overload. Colloids can be divided into natural colloids – human albumin solution and synthetic colloids – hydroxyethyl startch, dextran, and gelatin. Colloid solutions other than albumin are not routinely used because of lack of benefits, safety, and potential adverse effects.[27]

Indications of albumin administration:
Due to its intrinsic physiologic properties that make it ideal to use for certain critical care settings[28]

a. Sepsis: SAFE, Albios, and EARSS studies found that individuals in septic shock who received albumin resuscitation had better outcomes.[29] Surviving sepsis campaign guidelines suggest using albumin in patients who received large volumes of crystalloids
b. Acute respiratory distress syndrome (ARDS): It has been demonstrated that patients with ARDS who receive restricted fluid management which includes reducing fluid intake, using furosemide, and administering albumin have better oxygenation and reduced ventilation requirement but it did not affect patient outcome[30]
c. Spontaneous bacterial peritonitis (SBP): When albumin and antibiotics are used to treat SBP, incidence of AKI is reduced significantly
d. Hepatorenal syndrome (HRS): Combination of terlipressin and albumin is effective in the treatment of HRS
e. Large volume paracentesis (>5 L) – It is recommended to substitute 8 g of albumin for each liter of the ascitic fluid.[31]
    - *Post hoc* analysis of SAFE trial revealed that albumin administration was associated with increased mortality in patients with traumatic brain injury.[32]

PHASES OF FLUID MANAGEMENT

Following fluid resuscitation, it is crucial to recognize when to stop giving IV fluids, when to start the fluid evacuation, and when to end fluid removal. Four distinct phases or stages of fluid therapy were first proposed by Vincent and De Backer[33]-the salvage, optimization, stabilization, de-escalation concept, and later adapted to resuscitation, optimization, stabilization, and evacuation by Malbrain *et al*.[3]

Salvage/resuscitation phase

Fluids should be given liberally to ensure efficient resuscitation and maintain positive fluid balance. Target mean arterial pressure in the range of 60–65 mm of hg. Prefer isotonic fluid boluses and initiate vasopressors in parallel to achieve the desired MAP. In patients who require large volume of fluid administration albumin may be taken into consideration. Early vasopressor therapy and albumin administration help to minimize the need for crystalloids and consequent adverse

effects such as tissue edema. Simultaneously search for the source of shock and start the proper course of action. Secure invasive lines such as intra-arterial catheters and central venous catheters.[34]

Optimization

This phase starts where the patient remains hemodynamically unstable but no longer has relative or absolute hypovolemia. Patients will be under risk of fluid overload, therefore, fluids should be administered based on individual needs. To offer or to avoid fluids, utilize the fluid responsive markers such as PLR test, EEOT, PPV/SVV, CVP, echocardiographic assessment – inferior vena cava collapsibility/distensibility index, cardiac filling pressures. Echocardiography also helps in detecting the type of shock. The efficiency of therapy and coherence between microcirculation and macrocirculation can be assessed by serial measurements of lactate,[35] capillary refilling time, mottling score, scvo2/svo2, and V– A co2 gap. Maintain neutral fluid balance to maintain tissue perfusion.

Stabilization

As the term implies, the patient is hemodynamically stable hence, intensive bedside monitoring is not required. However, the patient may become unstable again due to secondary infection or insult and re-enter the rescue phase for which continuous monitoring is required till recovery. Maintain negative or neutral fluid balance. Continue organ support as needed.

De–escalation/evacuation

This is the last phase of resuscitation. Gradually wean the patient from vasoactive drugs and promote fluid removal. Fluid elimination will be usually achieved by spontaneous diuresis as the patient recovers. In the absence of spontaneous diuresis consider diuretics, if not responding consider RRT with ultrafiltration.

CONCLUSION

Fluid administration is the first line of management in patients presented with shock. Assessing preload responsiveness before giving fluid is essential, especially following the initial resuscitation phase. It has been proven that dynamic indices are a better predictor of fluid responsiveness than static measures. Clinicians should understand how to use them, and be conscious of their limits.

Crystalloid solutions should be used for most critically ill patients, but the choice between the crystalloid solutions remains less clear. Synthetic colloids (hydroxyethyl startch, dextran, and gelatin) should be avoided due to safety concerns. Albumin has a role in certain clinical conditions but it should be avoided in patients with traumatic brain injury. Like any other medication, fluids should be recommended with caution, and every attempt should be made to prevent their inappropriate administration.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Comparative evaluation of clinical outcomes of dexmedetomidine versus without dexmedetomidine in surgical field of otorhinolaryngology: A prospective study

ABSTRACT

Introduction: This prospective study aims to systematically compare the clinical outcomes of dexmedetomidine versus without dexmedetomidine in the context of nasal procedures. Dexmedetomidine is an Alpha-2 adrenergic agonist with sedative and analgesic properties. The research seeks to evaluate the impact of dexmedetomidine administration on surgical outcomes and patient safety.

Objective: Our research's objective was to evaluate the clinical outcomes of a bolus dose of dexmedetomidine during nasal surgery in the range of 0.5–1 μg/kg followed by maintenance infusion of dexmedetomidine at a dose of 0.2–0.5 μg/h compared to without dexmedetomidine.

Materials and Methods: This study is characterized as a prospective, observational, and comparative investigation. After institutional ethical committee approval, informed consent was obtained and 60 patients were split into two groups of 30 each. Group A received a dexmedetomidine bolus dose of 0.5–1 μg/kg diluted over 10 min in 0.9% normal saline followed by maintenance infusion of dexmedetomidine at 0.2–0.5 μg/h. Group B received routine anesthesia. In both the groups, infusions were titrated to maintain controlled hypotension. During the surgery, the bleeding score was determined using the Boezaart scale.

Results: In this study, it was observed that Group A had lower intraoperative blood pressure (BP), heart rate (HR), and mean arterial pressure which significantly reduced the overall bleeding score. In the dexmedetomidine group, the average Boezaart score was 2.0, and in Group B, it was 2.47. Both the groups experienced intraoperative complications in which medical intervention was carried out. Compared to Group B, Group A maintained better hypotension, eliminating both intraoperative and postoperative anxiety. Postoperatively BP, HR, respiratory rate, and SpO_2 were monitored till 5 h, and we found a significant difference ($P < 0.05$) between both the groups, where Group A demonstrated better hemodynamic stability.

Conclusion: The dexmedetomidine group demonstrated a substantial decrease in HR, mean atrial pressure, and intraoperative BP, resulting in a surgical field devoid of blood and with a lower bleeding grade. Postoperative problems were less common when dexmedetomidine was used.

Keywords: Boezaart scale, controlled hypotension, dexmedetomidine, nasal surgery, perioperative, postoperative complications, without dexmedetomidine

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INTRODUCTION

Chronic rhinosinusitis with a deviated nasal septum is treated by septoplasty, turbinoplasty, and functional endoscopic sinus surgery (FESS). The nasal surgery reestablishes the nasal cavity's ability to function properly. Intraoperative bleeding is

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seen more with sinonasal surgery because the mucosa of the nasal cavity has a rich vascular supply and is easily ruptured during surgery.[1,2] One strategy to minimize intraoperative blood loss and optimize the surgical field is controlled hypotension. An ideal hypotensive drug should possess the following qualities: ease of administration, quick onset and offset, quick elimination without harmful metabolites, and a steady dose-dependent action.[3] A 30% decrease in mean arterial pressure (MAP), i.e. MAP of 50–65 mmHg and systolic blood pressure (BP) of 80–90 mmHg, is deemed sufficient to maintain hypotension. Ear, nose, and throat surgeries present a significant challenge for both anesthesiologists and surgeons because of the region's rich vascularity, recurrent infections that can cause fibrosis, increased blood loss during the procedure, and small operating field. Controlled hypotensive anesthesia is becoming increasingly necessary due to endoscopic sinus procedures and microscopic surgery.[4,5]

Before using controlled hypotension, it is advised to do appropriate patient evaluation and selection, as well as correct placement and monitoring. Deliberate hypotension can be achieved by a variety of pharmacological agents, including magnesium sulfate, adrenergic beta-blockers (propranolol, esmolol, labetalol, and metoprolol), vasodilators (sodium nitroprusside, nicardipine, and nitroglycerine), inhalational agents (isoflurane, sevoflurane, and desflurane), intravenous α-2 agonists (dexmedetomidine and clonidine), and short-acting opioids (fentanyl, remifentanil, etc.). Propofol-infused total intravenous anesthesia is becoming increasingly common as a means of enabling controlled hypotension.[6,7]

A strong and extremely selective α-2 adrenoceptor agonist, dexmedetomidine, is a special sedative that has sympatholytic, analgesic effects without causing significant respiratory depression.[8] In addition to reducing postoperative opioid and antiemetic consumption, pain intensity, and the need for antiemetic therapy, intraoperative dexmedetomidine infusion improved the quality of recovery by reducing stress response.[9] Moreover, dexmedetomidine is becoming recognized as an effective therapeutic agent with a safe profile that can be used to treat a variety of clinical conditions.[8,9]

MATERIALS AND METHODS

The present investigation received approval from the institutional ethics committee before commencement. After informed consent was obtained, 60 patients who met the inclusion and exclusion criteria were enrolled between the ages of 12 and 60 who had physical status I and II according to the American Society of Anesthesiologists and were scheduled to undergo FESS, septoplasty, and turbinoplasty. Exclusion criteria included extensive illness state, two or more prior nasal sinus surgeries, extensive nasal mass, poor nothing by mouth (NBM) status (<6 h), hypersensitivity to study medications, and coagulation problems.

Decadron (8 mg), Tranexa (1 g), and Monocef (1 g) were administered to each patient before to surgery in order to lessen bleeding and minimize obstacles following the procedure. Using computer-generated random numbers, patients were randomly divided into two groups: Group A received dexmedetomidine at the dose of 0.5–1 μg/kg given over 10 min in 0.9%. Normal saline was followed by maintenance infusion at a dose of 0.2–0.5 μg/h, while Group B did not receive dexmedetomidine and anesthesia was maintained with induction medications. The anesthesiologist chose the anesthetic based on the patient's history, demographics, and severity of the illness. Preoperative vitals were monitored 1 h before the surgery, with an average BP = 115/75 mmHg, heart rate (HR) =82 bpm, respiratory rate (RR) =18 bpm, and SpO_2 = 98%. Baseline vitals were noted 15 min before surgery, average of BP = 125/80 mmHg, HR = 85 bpm, RR = 16 bpm, and SpO_2 = 98%. Following preoxygenation with 100% oxygen, both the groups were started on Ringer's lactate. Premedication with glycopyrrolate (0.2 mg/kg), fentanyl (2 μg/kg), and midazolam (0.5 mg/kg) in titrated doses, followed by bolus doses of propofol (2 mg/kg) and atracurium (0.5 mg/kg as bolus dose and maintained with titrated doses) for induction and sedation. Sevoflurane 2.5% was used to maintain anesthesia during the procedure and postintubation the oropharynx was packed with a throat pack. 15 min before the initiation of surgery, nasal packs soaked in 4% LOX solution with two ampoules of adrenaline were kept in the nasal cavity for decongestion. The surgeon used the Fromme–Boezaart scale to assess the quality of the surgical field. A 2.5 mg bolus dose of myopyrolate was administered to the patient to facilitate extubation following surgery. Patients were monitored for 5 h after surgery in the postsurgical intensive care unit. Any episode of hypotension (<60 mmHg) in both the groups was treated with an IV bolus of mephentermine (6 mg). In Group A, if BP was high (>120/80 mmHg), patients were given an infusion (0.25–0.5 μg/kg/h) along with a bolus dose of dexmedetomidine. In Group B, any rise in BP was treated with β-blockers.

Statistical analysis

The data were analyzed using descriptive analysis, which was done by mean and standard deviation for quantitative variables

and frequency and proportion for categorical variables. Statistical analysis was conducted utilizing SPSS software (IBM SPSS Statistics Version 22 Statistical Software: Core System Users' Guide. SPSS Inc. 2014). The independent sample *t*-test was used to compare the mean values between the research groups for quantitative parameters that were normally distributed (2 groups). Using the Mann–Whitney *U*-test (2 groups) or the Kruskal–Wallis test (>2 groups), medians and interquartile ranges for nonnormally distributed quantitative parameters were compared between research groups. $P < 0.05$ was deemed statistically noteworthy.

RESULTS

A total of 60 patients were enrolled who were divided into 2 groups, 30 in each. Patients' vitals were monitored intraoperatively for every 15 min till the end of surgery and postoperatively patients were monitored for 5 h for any episodes of bradycardia, tachycardia, hypotension, and hypertension.

The study group's demographics are shown in Table 1. Table 1 displays the statistical difference ($P < 0.05$) between the age categories, with a higher number of patients in the 18–39 age range and a higher proportion of male patients than female patients who had surgery. When dexmedetomidine was utilized, Group A's surgical time was shortened.

Table 2 represents the mean systolic BP (SBP) between both the groups. The data indicate that there was a statistically significant ($P < 0.05$) difference in SBP of both the groups at some intervals of time, but clinically no major difference was seen in both the groups. The dexmedetomidine group had reduced SBP compared to the group that did not receive dexmedetomidine.

Table 3 represents the mean diastolic BP (DBP) of both the groups. There was a statistically significant difference ($P < 0.05$) of DBP in both the groups, while at 165 min, statistical significance was seen. The dexmedetomidine group had a better reduction in DBP than the without dexmedetomidine group.

Table 4 represents the intraoperative HR in which the mean HR was statistically significant ($P < 0.05$) at some intervals,

Table 1: Demographic details between both the groups

Demographic details	Group A (dexmedetomidine group)	Group B (without dexmedetomidine group)	*P*
Age (years) (number of individuals)			
12–17	3	3	0.62
18–39	18	22	
40–59	6	4	
≥60	3	1	
Gender (number of individuals)			
Male	20	27	0.03
Female	10	3	
Duration of surgery (min) (mean±SD)	97.5±51.78	105.9±56.4	

SD: Standard deviation

Table 2: Comparison of mean systolic blood pressure between two groups

SBP at different time durations (min)	Study groups		*P*
	Group A (mmHg) (dexmedetomidine group), mean±SD	Group B (mmHg) (without dexmedetomidine group), mean±SD	
15	98.17±14.35	105.63±12.22	0.03
30	94.23±7.8	98.63±13.09	0.12
45	93.2±8.2	99.9±14.4	0.03
60	97.26±13.33	101.67±7.11	0.25
75	97.82±13.81	102.25±8.32	0.33
90	98.58±13.61	104.56±7.91	0.26
105	97.64±9.62	101.43±5.83	0.36
120	99.25±9.53	101.86±6.59	0.56
135	100.5±9.88	101±1.73	0.94
150	113±3	112±0	0.80
165	112.67±5.13	131±0	0.09
180	112±0	128±0	*

SBP: Systolic blood pressure, SD: Standard deviation

but clinically, we observed that Group A had reduced intraoperative HR compared to Group B.

Table 5 represents the intraoperative MAP in which 105 min and 165 min periods were noted to be statistically significant

Table 3: Comparison of mean diastolic blood pressure between two groups

DBP (min)	Study groups (mmHg)		*P*
	Group A (dexmedetomidine group), mean±SD	Group B (without dexmedetomidine group), mean±SD	
15	64.1±9.2	67.37±10.95	0.22
30	61.5±7.96	66.27±13.04	0.09
45	60.87±7.49	65.27±14.33	0.14
60	63.04±8.47	67.07±6.92	0.13
75	65.65±8.31	68.58±8.52	0.36
90	66.08±9.42	70.33±10.19	0.34
105	64.18±9.41	71.43±2.51	0.07
120	63.63±8.57	70.43±6.48	0.11
135	60±10.74	73±1.73	0.098
150	68±5.57	70±0	0.79
165	69.33±5.77	97±0	0.05
180	78±0	92±0	*

DBP: Diastolic blood pressure, SD: Standard deviation

Table 4: Comparison of mean heart rate between two groups

HR	Study groups (beats/min)		*P*
	Group A (dexmedetomidine group), mean±SD	Group B (without dexmedetomidine group), mean±SD	
15	81.63±14.39	82±13.06	0.92
30	82.2±13.26	76.67±6.21	0.04
45	82.43±12.41	76.03±5.69	0.01
60	83.39±10.34	80.69±9.42	0.41
75	79.94±12.47	79.77±9.01	0.97
90	82.92±8.49	81.6±10.61	0.75
105	82.82±13.86	78.29±5.68	0.43
120	77.38±6.16	76.14±7.08	0.72
135	83±4.08	74.33±0.58	0.02
150	82.67±11.24	82±0	0.96
165	84±16.97	85±0	0.97
180	76±0	82±0	*

HR: Heart rate, SD: Standard deviation

Table 5: Comparison of average mean arterial pressure between the two groups

MAP	Study groups (mmHg)		*P*
	Group A (dexmedetomidine group), mean±SD	Group B (without dexmedetomidine group), mean±SD	
15	75±9.57	76.9±13.17	0.53
30	72.37±7.5	72.73±15.77	0.91
45	72.03±6.79	72.73±14.28	0.81
60	74.26±9.52	77.93±6.28	0.20
75	75.71±8.74	76.92±11.71	0.75
90	76.83±9.58	81.33±9.22	0.29
105	74.27±7.25	81.14±3.63	0.04
120	73.63±6.46	80±5.23	0.06
135	71.25±9.25	82.33±0.58	0.10
150	82±3.61	84±0	0.68
165	82.67±4.62	108±0	0.04
180	85±0	95±0	*

SD: Standard deviation, MAP: Mean arterial pressure

($P < 0.05$), but clinically, the dexmedetomidine group had significantly reduced MAP compared to the without dexmedetomidine group.

Dexmedetomidine reduced intraoperatively vitals which subsequently reduced blood loss with an average bleeding score of 2.07 while without dexmedetomidine noted 2.47.

DISCUSSION

Nasal surgeries have a higher incidence of bleeding which can be reduced by lowering BP which improves clinical visibility, improves surgical outcome, and even reduces the risk of surgical complications and minimizes intraoperative blood loss. In this study, we compared otorhinolaryngology nasal procedures with dexmedetomidine versus without dexmedetomidine for controlled hypotension.

In a reported study, it was found that there was no statistically significant variation in the demographic or clinical characteristics in the group that received dexmedetomidine compared to the group that received remifentanil,[10] which is in line with this study. We could not find any statistical significance in terms of gender or demographics. The number of patients in the age group of 17 and 39 years were more likely to undergo nasal surgery as compared to patients in other age groups. In both the groups, BP and HR increased during and after the induction of anesthesia; however, in Group A, BP dropped more quickly than Group B after receiving a bolus dose of dexmedetomidine. Dexmedetomidine acts on postsynaptic α_2 adrenoreceptors in the central nervous system and inhibits sympathetic system activity, thereby reducing BP and HR.[11]

When nitroglycerine, propofol, and dexmedetomidine were compared as hypotensive medications in FESS, dexmedetomidine and propofol helped the patient achieve the goal blood pressure more successfully than nitroglycerine due to a lower heart rate in the dexmedetomidine group. Patients using dexmedetomidine and propofol during FESS saw reduced bleeding and quicker surgical times. Dexmedetomidine reached the target blood pressure faster than propofol,[12] which is consistent with our study. In Group A, after dexmedetomidine was administered as a bolus, SBP, DBP, and MAP began to decline and returned to the desired range after 5 min. However, at some intervals, it was observed that there was a statistically significant ($P < 0.05$) reduction in intraoperative SBP in both the groups, but clinically, dexmedetomidine reduced intraoperative SBP. The mean intraoperative DBP was also found to be significantly lower ($P < 0.05$) in Group A compared to Group B. It was observed that there was one case of hypertension in Group A which was treated with dexmedetomidine and two cases in Group B where medical intervention was performed by β-blockers.

In a reported study which evaluated esmolol and dexmedetomidine as means of hypotensive agents for FESS, both medications were noted to have significantly reduced MAP compared to baseline values. The preferred anesthetic approach in the esmolol group is relative bradycardia,[13] which is in link with our study. It was found to be statistically significant ($P < 0.05$) in MAP at some points between both the groups, but clinically, dexmedetomidine provided superior hypotension with decreased MAP compared to without dexmedetomidine. One patient in Group A who was a chronic smoker had an episode of reduced MAP which was at <50 mmHg, medical intervention was done with mephentermine.

Preoperatively, dexmedetomidine was studied to attenuate the pressor response and reduce the doses of opioids and anesthetics. The study compared dexmedetomidine with fentanyl and found that the mean HR was considerably lower in the dexmedetomidine group than in the fentanyl group,[14] which is correlated with our study. We observed a statistical significance at 30 min, 45 min, and 2:15 min ($P < 0.05$), but the mean HR was significantly lower in Group A. Preoperative anxiety was observed and was eliminated after dexmedetomidine administration in Group A compared to Group B. One case of tachycardia was observed in Group A which was treated with dexmedetomidine infusion and three cases in Group B which was treated with β-blockers.

A study comparing dexmedetomidine versus propofol-based anesthesia for controlled hypotension in sinus surgery found that the mean total blood loss in dexmedetomidine was significantly lower than propofol.[15] This finding is consistent with our study where we found a statistically significant difference ($P < 0.05$) in mean total blood loss where Group A was significantly lower than Group B.

Dexmedetomidine's better hypotension properties resulted in a lower Boezaart, surgical field grade, and better visibility of the surgical field during procedures, intraoperative BP, HR, and MAP were all reduced, which shortened the surgery's duration. Positioning the patient supine with their head raised to approximately 20° during surgery helps minimize intraoperative hemorrhage.

During our study, we found that persistent smokers had lower bleeding grades with dexmedetomidine use than without dexmedetomidine, while a few cases with hypertension, asthma, and diabetes underwent nasal surgery where we

recorded less bleeding grade without any complications in Group A than Group B [Figure 1].

Postextubation, all patients were monitored in the recovery room for adverse events of hypotension, hypertension, bradycardia, or tachycardia. There was a statistically significant difference ($P < 0.05$) in postoperative BP, HR, RR, and SpO_2 at different time intervals until 5 h. Group A demonstrated better hemodynamic stability than Group B. In patients of Group B, more local anesthetics, NSAIDs, antiemetics, and sevoflurane were used intraoperatively and Group A used less of these medications. Group B ($n = 20$) continued to receive ondansetron, tramadol, and NSAIDs after surgery, while Group A ($n = 4$) decreased their intake of ondansetron and NSAIDs.

In Group A, 6 and, in Group B, 22 patients had experienced complications. In Group B, out of 22 patients who experienced complications, 27.2% ($n = 6$) developed tachypnea, while in Group A out of 6 patients, 50% ($n = 3$) developed tachypnea. A patient with chronic asthma developed shortness of breath (SOB) 16.6% ($n = 1$) and medical intervention was done by asthalin puffs. No respiratory depression was seen in either group. Other complications that were seen in Group B includes cough 13.6% ($n = 3$), shivering 13.6% ($n = 3$), pain, 13.6% ($n = 3$), vomiting 13.6% ($n = 3$),agitation in 9% ($n= 2$) and 9% ($n=2$) experienced bleeding postoperatively. In Group A, apart from tachypnea and SOB, pain was noted in 16.6% ($n = 1$) patients. One patient with chronic HTN in Group A developed bleeding which was treated with the administration of amlodipine and fentanyl.

CONCLUSION

When comparing with dexmedetomidine and without dexmedetomidine, dexmedetomidine reduced BP, HR, and MAP which provided a clear, bloodless surgical field with less bleeding grade but also reduced the usage of propofol, sevoflurane, fentanyl, and other supportive medications. Postoperative incidences of complications were seen less in the dexmedetomidine group and had better hemodynamic stability in postoperative conditions than the without dexmedetomidine group.

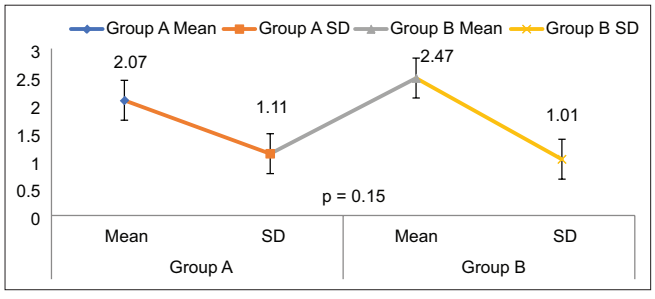

Figure 1: Mean Bleeding score using Boezaart surgical field grading scale between two groups.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

The clinical efficacy, outcomes and quality of life of diabetic disease patients treated with dapagliflozin

ABSTRACT

Introduction: Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease and a common serious complication that affects 1/3rd of type-1 and half of type-2 diabetes mellitus patients. In the early stages of DKD-RAAS blockades (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and antihyperglycemic agents such as sodium-glucose transport protein (SGLT) 2 inhibitors, glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors may help prevent DKD by lowering blood glucose levels and through intrinsic renal protection. SGLT2 inhibitors are a new class of oral antidiabetic drugs, which delay the progression of DKD. Dapagliflozin is a drug of choice when the estimated glomerular filtration rate (eGFR) is 25–75 mL/min/1.73 m^2 and urine albumin–creatinine ratio $\geq$30 mg/mmol.

Aim and Objectives: The aim of the study was to evaluate the clinical outcomes of dapagliflozin in DKD and to check the complications and quality of life of the patients after treatment.

Methodology: It was a prospective observational study conducted for a period of 6 months in a tertiary care hospital. The data were collected from the 49 patients with DKD who underwent treatment with dapagliflozin, after approval of the protocol by the IEC. The statistical analysis was done using SPSS software, V.22.(1) 1. SPSS I. IBM SPSS Statistics Version 22 Statistical Software: Core System Users' Guide. SPSS Inc. 2014.

Results and Discussion: The majority of patients enrolled were males (81.63%) compared to females (18.36%) and most of them were geriatrics > 60 years. The majority of patients received dapagliflozin 10 mg, followed by few patients with 5 mg. The effectiveness of dapagliflozin was observed by statistically significant improvement in serum creatinine ($P < 0.05$), BUN ($P < 0.05$), and blood urea ($P \leq 0.05$). Clinically significant improvement was observed in eGFR, creatinine clearance, serum sodium, potassium, chlorides, glycated hemoglobin levels, and body mass index ($P > 0.05$), which was statistically insignificant. Statistically significant improvement in the quality of life ($P < 0.001$) of patients was observed. Out of 49, two patients reported with UTI which may be a suspected drug-related side effect.

Conclusion: The study concludes that dapagliflozin has a positive impact on treating DKD. The overall quality of life of the patients was moderately improved. These outcomes suggest that dapagliflozin may become the main line therapy in patients suffering from DKD.

Keywords: Body mass index, dapagliflozin, diabetic kidney disease, estimated glomerular filtration rate, glycated hemoglobin

INTRODUCTION

Diabetic kidney disease (DKD) is the most frequent, burdensome, and expensive severe microvascular long-term complications of DM type 2. Moreover, it is characterized by persistent albuminuria and progressive decline in glomerular filtration rate (GFR), which eventually leads to irreversible renal damage and develops into end-stage renal disease (ESRD).[1-4] Diabetic nephropathy (DN) develops in conjunction with generalized microvascular illness and is frequently associated with macrovascular diseases such as

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cardiovascular, cerebrovascular, and peripheral artery disorders.[5] It is considered a microvascular complication and occurs in both diabetes mellitus type 1 and diabetes mellitus type 2. The disorder presents with persistent albuminuria and a progressive decline in the GFR. There is substantial evidence that early treatment can delay or prevent the progression of the disorder.[6] Diabetes, hypertension, elevated blood lipids, smoking, obesity, and glomerular hyperfiltration are the major risk factors of chronic kidney disease (CKD) and end-stage renal failure, accounting for nearly 50% of cases.[2,7,8] The progression of DN is predicated on changes in GFR and urine albumin excretion. It begins with hyperglycemia-induced glomerular hyperfiltration. Next is the silent stage followed by the third stage involving urinary albumin losses (30–300 mg/day) and the fourth stage is characterized by overt proteinuria (>300 mg/day). The fifth stage is end-stage kidney disease requiring renal replacement therapy.[9] Clinical basic treatment, including control of hyperglycemia, hypertension, and hyperlipidemia, stopping smoking, and changing diet, can reduce the proportion of diabetic patients reaching ESRD.[8] In the early stages of DKD-RAAS blockades (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers) and antihyperglycemic agents such as sodium-glucose transport protein (SGLT) 2 inhibitors, glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors may help prevent DKD by lowering blood glucose levels and through intrinsic renal protection.[9] A new class of diabetes drugs emerged in 2013, called SGLT2 inhibitors.[10] SGLT-2i can lower blood glucose by inhibiting sodium and glucose reabsorption by the renal proximal convoluted tubules, increasing urine glucose excretion, improving insulin

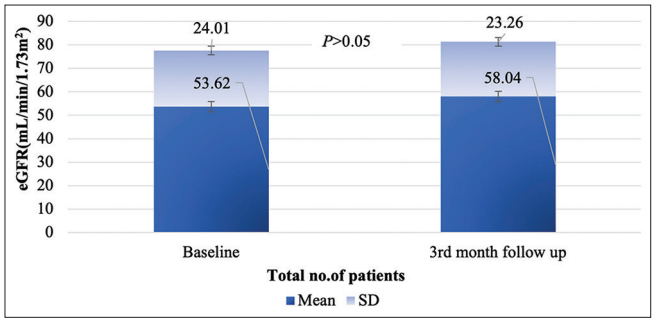

Figure 1: Estimated glomerular filtration rate in patients treated with dapagliflozin. SD: Standard deviation, EGFR: Estimated glomerular filtration rate

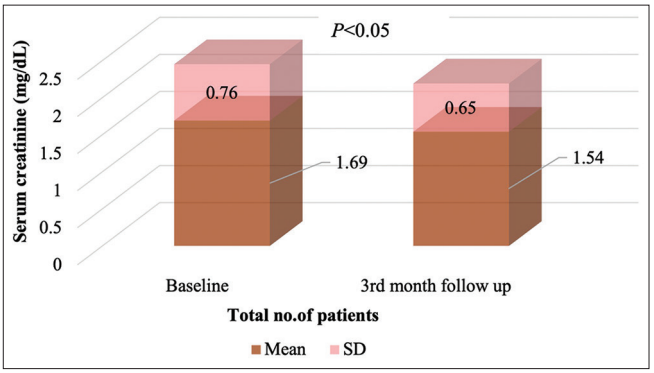

Figure 2: Serum creatinine in patients treated with dapagliflozin. SD: Standard deviation

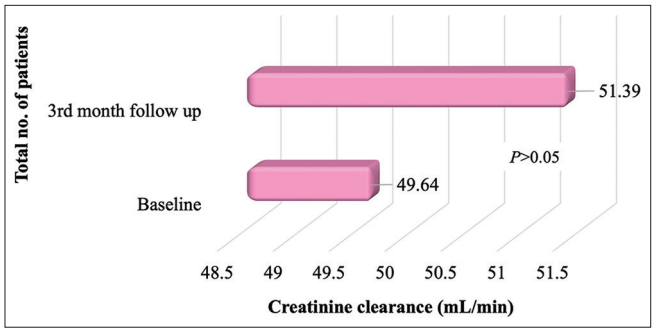

Figure 3: Creatinine clearance in patients treated with dapagliflozin

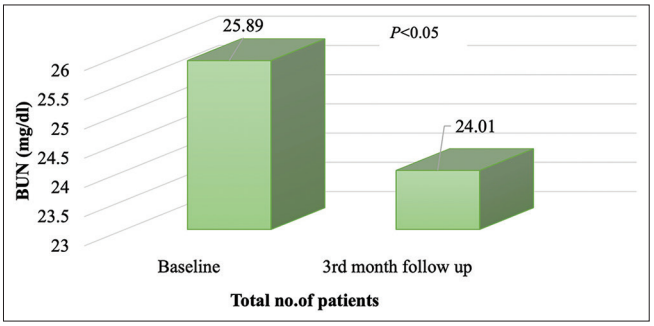

Figure 4: Blood urea nitrogen levels in patients treated with dapagliflozin. BUN: Blood urea nitrogen

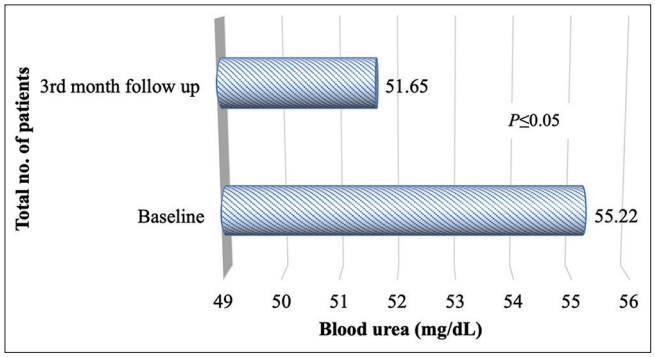

Figure 5: Blood urea levels in patients treated with dapagliflozin

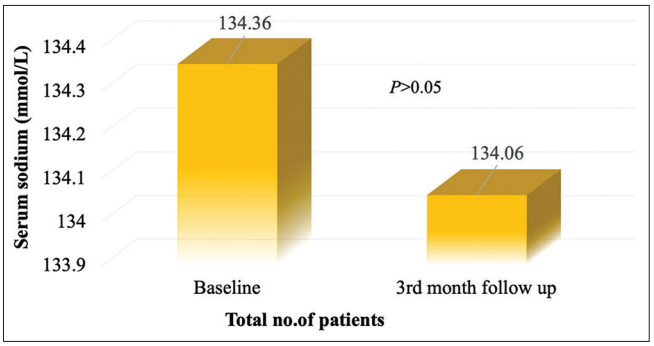

Figure 6: Serum sodium levels in patients treated with dapagliflozin

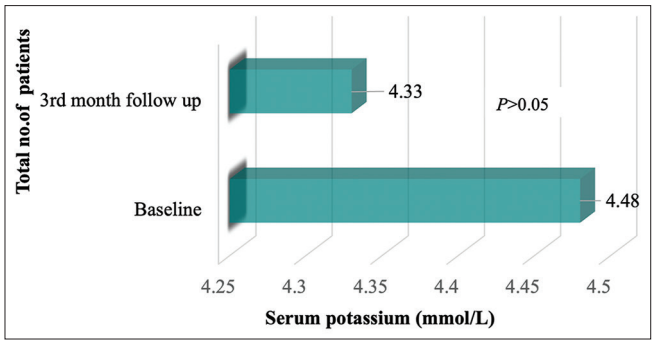

Figure 7: Serum potassium levels in patients treated with dapagliflozin

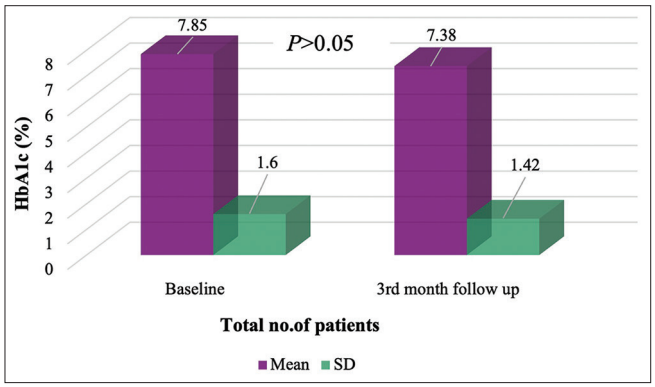

Figure 9: Glycated hemoglobin levels in patients treated with dapagliflozin. HbA1c: Glycated hemoglobin

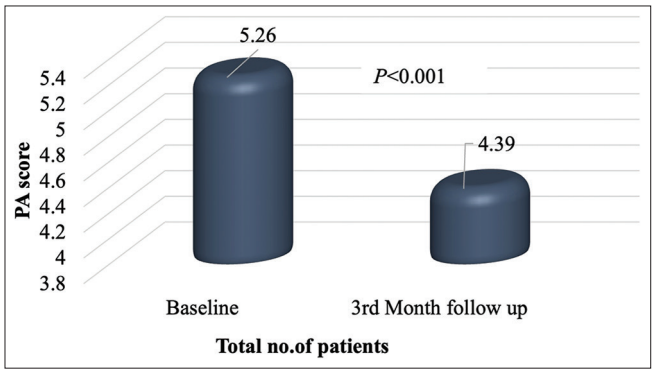

Figure 11: Physical activity score in patients treated with dapagliflozin. PA: Physical activity

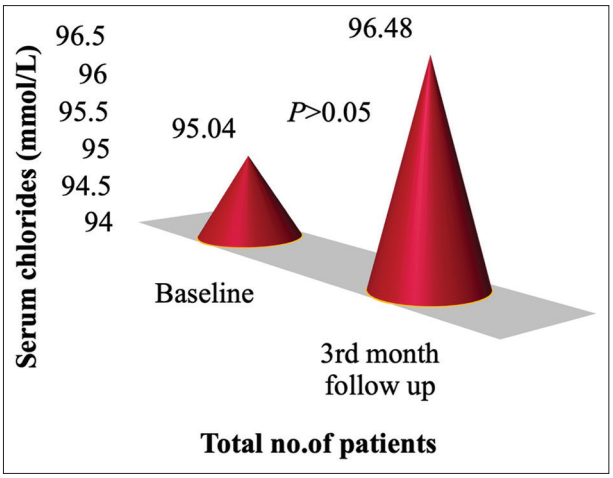

Figure 8: Serum chloride levels in patients treated with Dapagliflozin

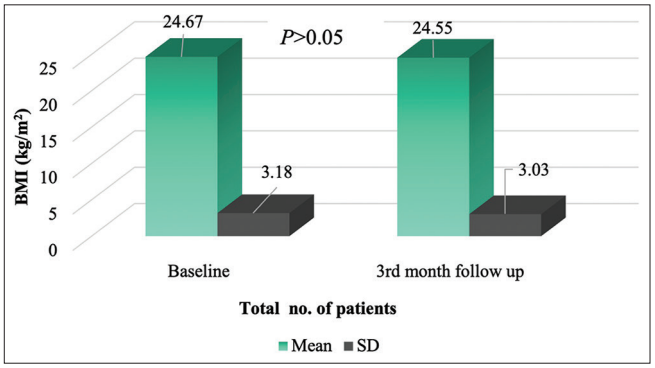

Figure 10: Body mass index in patients treated with dapagliflozin. SD: Standard deviation, BMI: Body mass index

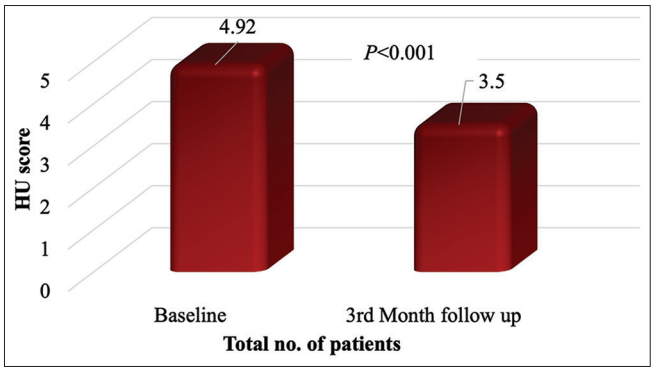

Figure 12: Health-care use score in patients treated with dapagliflozin. HU: Health-care use

resistance, and significantly reducing renal metabolic disorders caused by chronic hyperglycemia that allows the kidneys to dispose of excess blood glucose in the urine and reduce blood glucose, blood pressure, body mass index, and exert protective effects on DKD by inhibiting the proximal tubule reabsorption of filtered glucose load, blocking immune cell activation and inflammatory responses. Furthermore, SGLT-2i enhances sodium excretion in renal tubules, resulting in a diuretic action that reduces body fluid volume and blood pressure, hence lowering glomerular ultrafiltration.[11] By inhibiting SGLT2, dapagliflozin blocks the reabsorption of filtered glucose in the kidney, increasing urinary glucose excretion and reducing blood glucose levels.[12] Dapagliflozin is an SGLT2i that has been shown to decrease glycated hemoglobin (HbA1c) by promoting urinary glucose excretion, body weight, systolic blood pressure, and albuminuria.[12]

METHODOLOGY

This study is a prospective observational single-center study. The study data were gathered and informed consent was obtained in accordance with the Declaration of Helsinki.

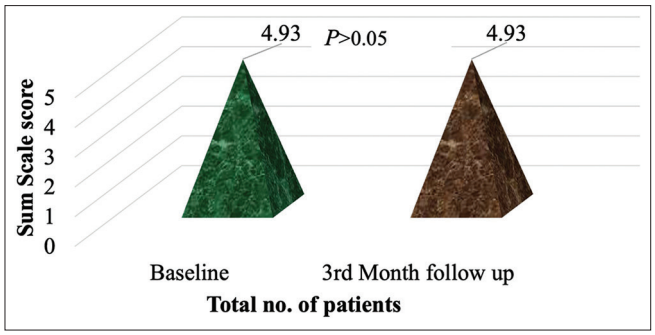

Figure 13: Sum scale score in patients treated with dapagliflozin

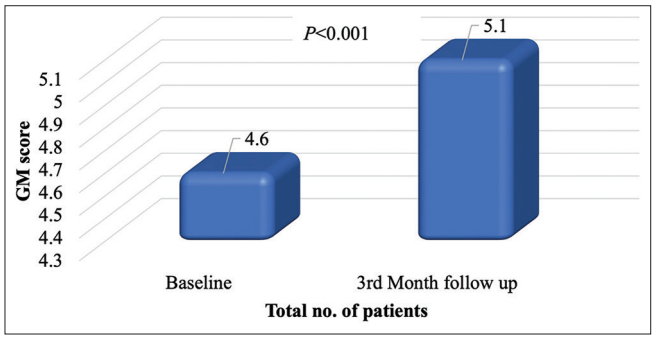

Figure 14: Glucose management score in patients treated with dapagliflozin. GM: Glucose management

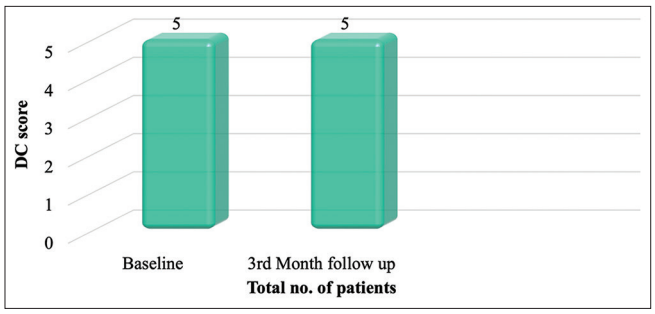

Figure 15: Dietary control score in patients treated with dapagliflozin. DC: Dietary control. DC: Dietary control

The study conduct was approved by the Institutional Ethics Committee. A sample size of 49 patients was enrolled and provided with written informed consent before participating. The study was conducted for a period of 6 months. This study was conducted at tertiary care hospital, Hi-Tech City, Hyderabad.

Inclusion and exclusion criteria

Patients with DKD or type 2 diabetes with chronic kidney disease at the study center were examined by consultant nephrologists and general physicians. Subjects receiving dapagliflozin and meeting other inclusion criteria were enrolled in the study.

Inclusion criteria

- Patients with Stage 2 to Stage 4 CKD with type 2 diabetes
- Patients aged above 18 years
- All genders
- Patients from outpatient and inpatient departments.

Exclusion criteria

Included patients on:

- Renal dialysis (stage 5 CKD)
- Patients with renal replacement therapy
- Gestational diabetes mellitus
- Patients receiving anticancer treatment
- Patients with immunosuppression.

Criteria for evaluation

The following parameters will be monitored throughout the study. Follow-up of the patients would be done 0–3–6 months to see the following parameters: estimated GFR (eGFR), serum creatinine, creatinine clearance, BUN, blood urea, serum uric acid, electrolytes, HbA1c, body mass index (BMI), and urine infections (bacterial and fungal). In quality of life: glucose management, dietary control, physical activity, and health-care use.

Statistical method

The change in the quantitative parameters and before and after the intervention was assessed by paired *t*-test (In case of two time periods). $P < 0.05$ was considered statistically significant. The statistical analysis was done using SPSS software, V.22.(1) 1. SPSS I. IBM SPSS Statistics Version 22 Statistical Software: Core System Users' Guide. SPSS Inc. 2014.

RESULTS

Demographic details

According to age, adults (18–59 years) are 38.77% and geriatrics (>60 years) are 61.22%, and overall gender analysis 40 males (81.63%) and females are 9 (2.04%).

DISCUSSION

The single-center prospective observational study was conducted on patients with DKD who were treated with dapagliflozin for a period of 6 months in 49 individuals [Table 1]. The majority of the patients enrolled in this study were above 60 years, mean age was found to be 62.02 ± 9.80 years. According to our study, male patients 81.63% were more enrolled than female patients 18.36%. Overall individuals' eGFR levels improved before and after the treatment which was statistically not significant ($P > 0.05$). It was consistent with a reported study where dapagliflozin raises eGFR levels after treatment which was statistically insignificant ($P > 0.05$) [Figure 1].[13] Serum creatinine is decreased (1.69 ± 0.76 mg/dL) and after

Table 1: Comparison of dapagliflozin in diabetic kidney disease before and after the treatment

Characteristics ($n=49$)	Before treatment (x±s)	After treatment (x±s)	*P*
eGFR (mL/min/1.73 m^2)	53.62±24.01	58.04±23.26	>0.05
Serum creatinine (mg/dL)	1.69±0.76	1.54±0.65	<0.05
Creatinine clearance (mg/dL)	49.64±23.38	51.39±20.36	>0.05
BUN (mg/dL)	25.89±17.32	24.01±15.58	<0.05
Blood urea (mg/dL)	55.22±37.14	51.65±33.61	≤0.05
Serum sodium (mmol/L)	134.36±7.35	134.06±4.78	>0.05
Serum potassium (mmol/L)	4.48±0.59	4.33±0.51	>0.05
Serum chlorides (mmol/L)	95.04±6.21	96.48±5.40	>0.05
HbA1c (%)	7.85±1.60	7.38±1.42	>0.05
BMI (kg/m^2)	24.67±3.18	24.55±3.03	>0.05

eGFR: Estimated glomerular filtration rate, HbA1c: Glycated hemoglobin, BMI: Body mass index, BUN: Blood urea nitrogen

the treatment (1.54 ± 0.65 mg/dL) which was statistically significant ($P < 0.05$) [Figure 2], which is corresponding to the reported study where a reduction in serum creatinine was noticed before (143.08 ± 36.33 μmol/L) and after treatment (104.10 ± 24.68 μmol/L).[14] On creatinine clearance in DKD, no trials had been previously reported hence no data were found. In our investigation, after the treatment, increase in creatinine clearance was seen with significance difference of $P > 0.05$ [Figure 3]. On blood urea nitrogen and blood urea in DKD, no additional investigations had been previously reported. In our study, we observed that a substantial decrease in BUN ($P < 0.05$) and blood urea ($P \leq 0.05$) levels after the treatment which was statistically significant [Figures 4 and 5]. Serum sodium levels decreased slightly and there was no significant ($P > 0.05$) change, which was similar to the previously reported study.[14] Here, we observed that the effect of dapagliflozin does not affect sodium levels [Figure 6]. Serum potassium levels fluctuate within the normal range and were seen a slight drop after treating, which was insignificant ($P > 0.05$) [Figure 7]. However, in the reported study, no change in potassium levels when treating with dapagliflozin and empagliflozin, but a small increase in potassium levels was seen with canagliflozin.[14] Serum chloride levels were slightly increased after treatment, which was not significant ($P > 0.05$) [Figure 8]. There were no studies reported earlier on chloride levels in DKD. Based on the electrolyte changes observed above, it is assumed that dapagliflozin has minimal effect on the electrolyte changes in patients suffering from DKD. The overall HbA1c levels decreased after the treatment, indicating that dapagliflozin's effectiveness was noted and that the rate of disease development was reduced but it was not significant ($P > 0.05$) when compared with previously reported study HbA1c was reduced and which is significant ($P < 0.05$) [Figure 9].[3] A decline in BMI was seen in all the patients after treating, which was complementary to other reported studies [Figure 10].[3,14]

Using the Diabetes Self-Management Questionnaire, we evaluated the overall quality of life of the patients which includes how patients managed their diet, physical activity, and occupational tasks. In the current study, we found that scoring of glucose management, physical activity, and health-care use was significant $P < 0.001$ [Figures 11 and 12]. No significant difference was found in dietary control. When combined with all the scores, the sum scale score was insignificant $P > 0.05$ [Figure 13]. The current study is similar to the previously reported study where all subscales were significant ($P < 0.05$) [Figures 14 and 15], but when compared with our study, glucose management, physical activity, and health-care use were significant.[14] Dietary control counseling is necessary for patients to reduce their risk of developing DKD. After the treatment, dapagliflozin reported a lower rate of adverse events such as UTI which was observed in only 2 (4.08%) patients. No other severe adverse reactions were found in the enrolled patients which indicates that dapagliflozin has a lower incidence of adverse reactions. In previously reported study, 3 (5%) out of 60 patients were reported with UTI which was analogous to the present study.[3]

CONCLUSION

The present study concludes that dapagliflozin has a positive impact on treating DKD. The overall quality of life of the patients was moderately improved might be due to the shorter duration of the study. In the future, dapagliflozin may become the main line therapy in patients suffering from DKD. Further studies are needed to substantiate the clinical outcomes of this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Haemothorax after primary percutaneous coronary intervention for aborted cardiac arrest with cardiopulmonary resuscitation

ABSTRACT

Cardiopulmonary resuscitation (CPR) is an irreplaceable option in patients with sudden cardiac arrest. However, lifesaving CPR can also put the patients and treating physicians in a predicament with certain rare and life-threatening complications due to chest wall injuries. Hemothorax is one of such complications which must be diagnosed and treated as early as possible, more importantly in patients with acute coronary syndrome (ACS) as a cause of cardiac arrest, wherein antithrombotic drugs are on board. Possible sources of bleeding in hemothorax can be injury to the internal mammary artery (IMA), intercostal arteries, or rarely azygos vein. Careful evaluation for the source of the bleeder is necessary as often bleeders may be missed out in early phase of evaluation due to associated hemodynamic factors such as low mean arterial pressure, raised intrathoracic pressures, and vasospasm. Here, we report a case of ACS with sudden cardiac arrest revived by CPR and primary percutaneous coronary intervention who eventually developed hemodynamically significant hemothorax due to the right IMA injury as detected by catheter-mediated angiography, which was subsequently sealed by vascular microcoils at either ends of the perforated segment.

Keywords: Cardiopulmonary resuscitation, coil embolization, digital subtraction angiography, hemothorax, intercostal drainage

INTRODUCTION

Acute myocardial infarction (MI) is one of the most common causes of cardiac arrest requiring cardiopulmonary resuscitation (CPR) with a cumulative incidence of 9.8% in 12 years (0.8% annually).[1] Around 22% of patients achieve a return of spontaneous circulation (ROSC) after CPR in acute MI.[1] CPR is not always innocuous, it is associated with complications such as sternal fractures (24%) and lung contusion (20%), and rarely it can lead to hemothorax (10%).[2] The bleeding sources for hemothorax can be the internal mammary artery (IMA), azygos vein, intercostal arteries, and veins.[3] In patients with acute coronary syndrome (ACS), bleeding can be further exacerbated due to concomitant use of antiplatelets, anticoagulants, or IV GP11B/IIIA inhibitors. The bleeders may be missed out in some patients during the early phase of evaluation due to associated hemodynamic factors; therefore, careful reassessment is important in diagnosing this condition to embark on specific therapeutic intervention. Here, we report a case of ACS with cardiac arrest revived by CPR, and primary percutaneous coronary intervention (PCI) was done to the right coronary artery (RCA) under dual antiplatelets and IV GPIIB/IIIA inhibitors, who

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subsequently developed hemodynamic instability with hemothorax 2 h after procedure.

CASE REPORT

A 57-year-male, hypertensive, nondiabetic came to the emergency room with acute chest pain for 30 min. He was hemodynamically stable, and an electrocardiogram (ECG) revealed acute ST-segment elevation inferior wall myocardial infarction with corresponding wall motion abnormality and good Left ventricle (LV) function on echo.

When preparing for primary PCI, he had a cardiac arrest (mention the type of arrest) and ROSC was achieved within 5 min of CPR. In the process, he was intubated and connected to a mechanical ventilator, a central line was placed through Rt internal jugular vein, and two cycles of IV adrenaline and atropine were given. Manual CPR was performed alternatively by two emergency physicians standing on either side of the patient couch. As ROSC was achieved, he was shifted to the cath lab for a coronary angiogram (CAG), followed by revascularization. CAG revealed acute total occlusion of RCA which was revascularized by thrombosuction and 3.5/38 mm Xience Expedition stent placement [Figure 1 and Video 1]. Postprocedure, he was shifted to the intensive critical care unit (ICU) for further care. He was given loading doses of clopidogrel and aspirin after CAG and started on injection tirofiban to cover the window of lack of antiplatelet activity. When in ICU, 2 h later, his mean arterial pressure (MAP) started dropping with increasing heart rate and inotropes were initiated for maintaining MAP. ECG and echo did not show any signs of ischemia or LV dysfunction. Chest X-ray revealed a whitening right thoracic field and mediastinal shift to the left along with a hemoglobin drop by 3 gm/dl. Due to the rapidity of hemodynamic deterioration and suspected arterial injury, we took him to the cath lab and confirmed the patent stent by doing CAG followed by catheter exploration for bleeder identification.

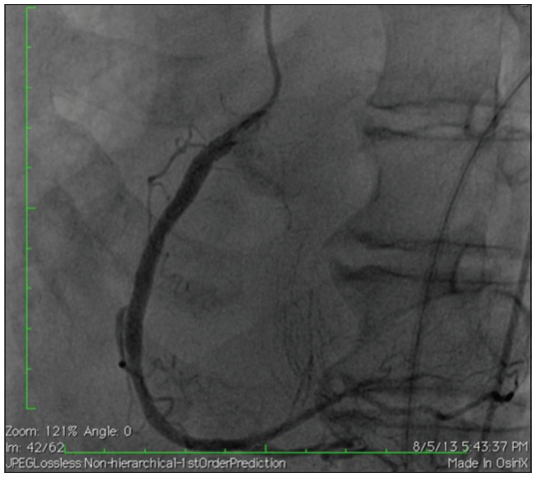

Figure 1: Postright coronary artery Stenting

Digital subtraction angiography (DSA) and angiography of the right IMA were done [Figure 2a, b and Video 2a, b], but could not find any extravasation. DSA of posterior intercostal arteries was performed, but extravasation could not be found [Figure 2c]. As the right hemothorax is tense with mediastinal shift, intercostal drainage (ICD) was inserted by a cardiac surgeon within the cath lab and drained around 750 ml of blood. Post-ICD, DSA of the right IMA revealed extravasation from the distal site [Figure 3a and Video 3a]. Successful coiling of artery was performed from either side of perforation with 3 mm 0.018 Hilal embolization microcoils (Cook, USA) [Figure 3b and Video 3b]. Postembolization, 300 ml of drainage came from the right ICD, followed by a dry tap after 24 h. Hemoglobin level stabilized after embolization and 2 units of packed cells. ICD removal was done on day 2 followed by extubation and discharge from the hospital on day 5.

DISCUSSION

Sudden cardiac arrest complicating ACS is a known entity requiring CPR for maintaining circulation. Although it is a lifesaving procedure, CPR can be associated with significant chest wall injuries, especially when carried out at higher depth, prolonged duration, and by nonphysicians. Hemothorax is observed in 10% of patients, commonly because of injury to IMA, intercostal arteries and veins, and azygos veins.[3] Bleeding can be accentuated in ACS scenarios due to antithrombotic drugs. This should be considered in situations of unexplained drop in blood pressure or hemoglobin, respiratory distress, rise in jugular venous pressure (JVP), and dull percussion notes on the chest. Careful evaluation for bleeders is recommended as they may be missed out in the initial angiogram or DSA due to the sealing off by high intrathoracic pressures, blood vessel spasm coupled with low MAP, or bleeding rate less than the detectable threshold of the respective investigation involved.[4] Therefore, reassessment for bleeder after correcting hemodynamic factors is mandatory in cases of angiographic misses. Sometimes, ICD insertion to drain hemothorax would reduce the mean thoracic pressure and improve the MAPs and may reveal the bleeder on subsequent angiography. The usual vessels to be evaluated are IMA, intercostal arteries on the affected side, and azygos vein. Central line-induced causes also need to be considered in differential diagnosis. The usual location of vascular injuries is in and around rib fractures or midsternum where the shear stress is maximum.[5] IMA trauma leading to extravasation is an uncommon entity, but is reported

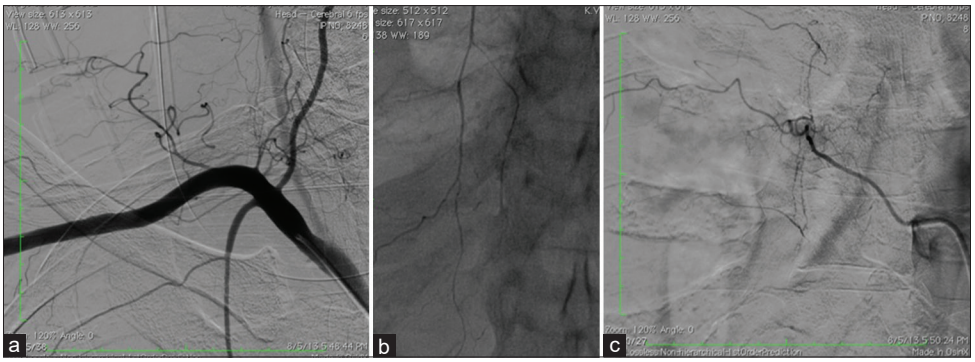

Figure 2: (a) No extravasation seen in digital subtraction angiography proximal part of subclavian. (b) No extravasation seen in from distal internal mammary artery. (c) No extravasation from one of the Rt posterior intercostal arteries

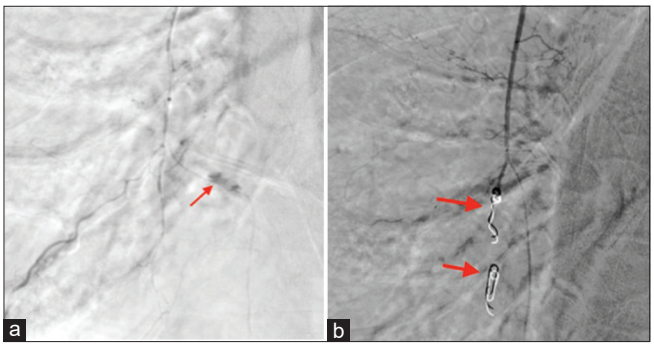

Figure 3: (a) Internal mammary artery (IMA) extravasation of contrast seen after intercostal drainage drainage (arrow). (b) Final digital subtraction angiography of IMA after coiling on either side of the perforated segment (Arrow indicates coil position on either side of bleeder)

in the literature.[6] The high blood flow rate in IMA around 150 ml/min (RCA - 35 ml/min and left anterior descending artery [LAD] - 65 ml/min) can lead to a rapid deterioration of hemodynamics.[7] Transcatheter embolization is the therapy of choice in these patients for quick hemostasis and to minimize the number of transfusions. In IMA injuries, embolization of the artery should be performed on either side of perforation to prevent further bleeding from retrograde collateralization from an inferior epigastric artery. Early identification and treatment of this condition would minimize the need for blood transfusions and reduce morbidity and mortality.

CONCLUSION

Hemothorax post-CPR is an uncommon entity, but heightened clinical suspicion is recommended in scenarios of unexplained hemodynamic deterioration. Either computed tomography angio or catheter-mediated selective angiogram is performed to unearth the bleeder. In case of failure to identify bleeder, reexamination after hemodynamic correction is strongly recommended. IMA bleeding must be coiled on either side of perforation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

SGLT2 inhibitor-induced ketoacidosis – A diagnostic challenge

ABSTRACT

Diabetic ketoacidosis is rarely caused by sodium-glucose cotransporter-2 (SGLT2) inhibitors and can be difficult to recognize. A 56-year-old male patient, with a body mass index of 31.87 and a long-standing history of diabetes mellitus, presented with acute gangrenous cholecystitis and was treated with intravenous antibiotics. Empagliflozin and metformin were started for blood sugar control. Four days after surgery, he presented with nausea and vomiting. He was found to have deep and labored breathing following upper gastrointestinal endoscopy. Labs revealed severe ketoacidosis with normal blood sugars. He was hydrated well with no improvement in metabolic acidosis. Empagliflozin was stopped, intravenous insulin and dextrose infusions were started, and his acidosis was corrected rapidly. SGLT2 inhibitors are associated with an increased risk of diabetic ketoacidosis (DKA). The absence of substantial hyperglycemia potentially delays the diagnosis. The stress of recent surgery likely precipitated DKA in this patient. It is important to consider the diagnosis of euglycemic DKA in patients receiving empagliflozin and presenting with nausea and vomiting, especially in the immediate postoperative period.

Keywords: Empagliflozin, ketoacidosis, postoperative, sodium-glucose cotransporter-2, surgery

INTRODUCTION

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are relatively newer antihyperglycemic drugs. They reduce renal tubular glucose reabsorption. They favorably affect blood pressure and weight. We report a case of clinically severe ketoacidosis, precipitated by empagliflozin.

CASE REPORT

A 56-year-old obese (body mass index = 31.87 kg/m^2) Indian male was incidentally found to have diabetes mellitus on a routine checkup 12 years ago. He was using oral hypoglycemic drugs (glimepiride 4 mg/day, metformin 2000 mg/day, voglibose 0.4 mg/day, and teneligliptin 20 mg/day).

He presented with fever, abdominal pain, nausea, and vomiting for 5 days before admission. On physical examination, right hypochondriac tenderness was present. White blood cell count was 22K. HbA1C was 11%. The random blood sugar was 257 mg/dL. Contrast-enhanced computed tomography abdomen showed emphysematous cholecystitis with a focal defect in the fundus of the gallbladder with multiple small fluid collections. The patient was given piperacillin-tazobactam, intravenous fluids, and insulin during the hospital stay. Symptoms resolved and leukocytosis improved. The patient was not

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comfortable taking insulin at home and was switched to oral empagliflozin 12.5 mg per day and tablet metformin 1000 mg per day. The patient was recommended an interval cholecystectomy after 4–6 weeks.

Several weeks later, laparoscopic placement of a cholecystostomy tube was done, and 4 days later, he had recurrent vomiting without fever, abdominal pain, or jaundice. Liver function tests were normal. *Magnetic resonance* cholangiopancreatography abdomen showed no inflammation of the gallbladder or choledocholithiasis. Fasting blood sugar was 115 mg/dL. Urine was positive for ketones on the dipstick. Upper gastrointestinal endoscopy to evaluate for peptic ulcer disease revealed edematous duodenum only.

The patient was found to have fast deep breathing during recovery from anesthesia administered during endoscopy. An arterial blood gas (ABG) analysis showed a pH of 7.13, bicarbonate of 6 mmol/L, and normal lactate.

The random blood sugar at that time was 127 mg/dL. The patient was given a total of 7 L of fluids, including 3.5 L of Ringer's lactate and 3.5 L of oral fluids for the next 24 h. The patient continued to vomit. A repeat ABG showed persistent metabolic acidosis with a pH of 7.15 and bicarbonate of 10 mmol/L.

Euglycemic diabetic ketoacidosis (DKA), precipitated by empagliflozin, was suspected. Empagliflozin was stopped. The patient was given intravenous insulin infusion and dextrose saline infusions. Within 24 h, his blood pH normalized, and he became asymptomatic. He has been using sitagliptin and metformin, and SLGT2 inhibitors were discontinued.

DISCUSSION

SGLT2 inhibitors are associated with an increased risk of DKA, as shown in multiple trials.[1,2] SGLT2 inhibitors increase the production of ketones and increase renal absorption of ketones. The absence of substantial hyperglycemia potentially delays the diagnosis.[3] In Asians with type 2 diabetes mellitus, the incidence of DKA with SGLT2 inhibitors was reported to be low.[4,5]

The stress of recent, sepsis, and surgery precipitated DKA in our patient. Further delay in diagnosis is potentially dangerous. Several authors recommend discontinuing SGLT2 inhibitors 3 days before elective surgery.[6,7]

CONCLUSION

If a patient has ketoacidosis with normal blood sugar and is taking an SGLT2 inhibitor, consider stopping the medication. Clinicians should be aware of the presentation and treatment of euglycemic DKA.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Congenital muscular torticollis

ABSTRACT

Torticollis is a clinical condition in which there are head tilt on the affected side and chin lift toward the contralateral side. Congenital muscular torticollis is the second most common cause of congenital musculoskeletal deformities. Torticollis is one of the most common causes of postural deformity. Congenital muscular torticollis is the most common cause of torticollis, others being nonmuscular causes. The incidence of congenital muscular torticollis is ranging from 0.2% to 3%. We report a 3-year-old female child with muscular torticollis with facial asymmetry. The child was investigated. Computed tomography was normal. The child was treated with sternocleidomastoid release. In this case, we emphasize the importance of early diagnosis and early intervention.

Keywords: Congenital, craniofacial, musculoskeletal, sternocleidomastoid, torticollis

INTRODUCTION

Congenital muscular torticollis is ipsilateral cervical flexion and contralateral cervical rotation due to the shortening of sternocleidomastoid muscle with or without mass. Craniofacial asymmetry develops involving the eyes, ears, and mandible.[1,2] If untreated, craniofacial deformities, cervical spine dysraphism, and painful limited cervical motion develop requiring complicated surgeries.[3]

Etiology of Congenital Muscular Torticollis (CMT) has no proven causes or pathology. Birth trauma,[4] prenatal or perinatal compartment[5] syndrome has been attributed as various causes. Advanced testing such as immunohistochemical and gene expression provide a strong evidence of intra uterine impairment of development of Sternocleidomastoid muscle.[6]

Congenital muscular torticollis diagnosed early and when physiotherapy initiated has better outcomes. If presented late it requires Sternocleidomastoid lengthening or release.

CASE REPORT

A 3-year-old female child was referred from the peripheral center to the surgical outpatient department in view of head tilt toward the right side observed by parents from 1 year of age. The child has complaints of pain. The child was born out of nonconsanguineous marriage and spontaneous conception to a primi mother. Antenatal scans were normal. The child was delivered vaginally in breech presentation with difficult extraction of the head. The child cried after stimulation. Postnatally, the baby did not require neonatal intensive care unit admission. Developmental milestones are normal.

On examination, restricted movements were observed. Facial asymmetry with small eyes and small maxillary and mandibular prominence was observed [Figure 1]. On palpation, no tenderness was noted. Computed tomography (CT) scan of the cervical spine was done and

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was normal. Sternocleidomastoid muscle release [Figure 2] on the right side was done after a detailed preanesthetic checkup.

DISCUSSION

Torticollis is also called as wry neck or twisted neck. Torticollis classified into two types, Muscular and Non muscular torticollis. Congenital muscular torticollis is a benign condition. Congenital muscular Torticollis is the second most common cause of congenital musculoskeletal deformities[7] congenital muscular torticollis classified into three types as postural(20%), muscular(30%) and sternocleidomastoid mass (50%). Nonmuscular types are ocular, rheumatological, and neurogenic causes.[8-10] Congenital muscular torticollis is a common postural deformity. The incidence of Congenital muscular Torticollis is ranging from 0.2%-3%.[11] When neglected can lead to facial asymmetry. Delayed recognition and treatment requires complicated surgery. In this article along with reporting the case we managed, we emphasize the role of early detection and treatment modalities.

An early detection in a newborn by performing a full cervical range of motion can detect torticollis. An early intervention at this point by neck stretching exercises and tummy time has resolved torticollis. When the physical therapy has not given results or the child presents at delayed age, physical therapies might not be helpful and require surgical management. Before surgical management, nonmuscular causes should be ruled out by ultrasonography or CT neck. Surgical options include bipolar release or sternocleidomastoid and *Z* lengthening. A systematic review and meta-analysis on the effectiveness of surgical treatment done by Kim *et al*. suggests that surgical treatment for neglected congenital muscular torticollis has satisfactory.[12]

Here we report a child presented to us at 1 year of age with congenital muscular torticollis. The sternocleidomastoid release was done [Figure 3]. The child will be followed up with physiotherapy and regular assessment of correction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

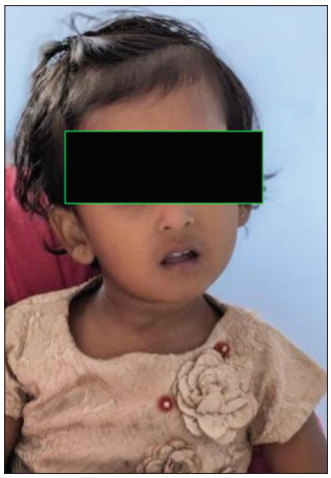

Figure 1: Preoperative

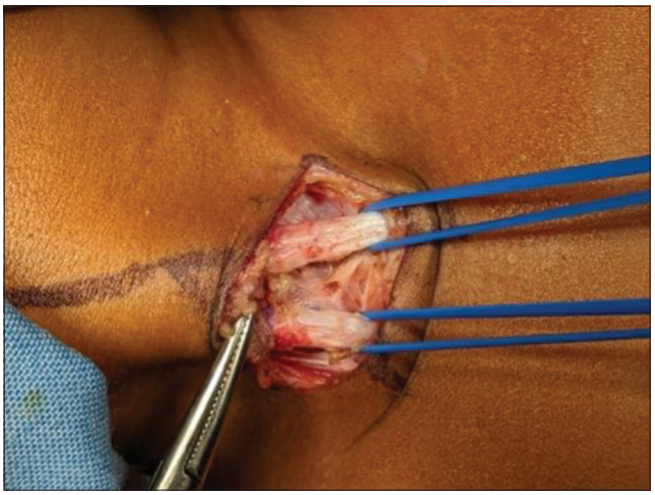

Figure 2: Intraoperative exposure of two heads of sternocleidomastoid muscle (SCM)

Figure 3: Postoperative

Conflicts of interest

There are no conflicts of interest.

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Case Report

Primary small-bowel gastrointestinal stromal tumor presenting with severe anemia: A report of two cases

ABSTRACT

Gastrointestinal stromal tumors are rare mesenchymal neoplasms that commonly occur in the stomach and small intestine and can occur anywhere from the esophagus to the anus. We are reporting two cases with identical presentations of severe anemia and abdominal discomfort, which revealed the diagnosis of primary small-bowel gastrointestinal stromal tumour (GIST), on computed tomography (CT), as standard endoscopy investigations failed to reveal the cause for the anemia. Both patients underwent surgical resection for the lesions and histopathological examination confirmed the diagnosis of GIST. After surgical management, hemoglobin levels of both patients improved, and were discharged with uneventful postoperative course. These case reports stress the importance of contrast-enhanced computed tomography (CT) scans, for investigating anemia, along with the standard endoscopy tests.

Keywords: Anemia, colonoscopy, computed tomography, endoscopy, gastrointestinal bleeding, gastrointestinal stromal tumors

INTRODUCTION

Gastrointestinal stromal tumor (GIST), first described by Mazur and Clark1983,[1] is the most common mesenchymal neoplasm of the GI tract; however, it accounts for <1% of all GI tumors.[2] It originates from the interstitial cells of Cajal, which are part of the autonomic nervous system of the intestine.[3] The majority of the lesions are benign with a possibility of 20%–30% for malignancy.[4] On the whole, sarcomas of the small intestine are identified as GISTs. The majority occur in the stomach and small intestine, although they can occur anywhere from the esophagus to anus.[5] About 10% arise outside of the GIT, for example, the pancreas, retroperitoneum, or mesentery: a small proportion arise in locations giving rise to incorrect preoperative diagnoses.[6] There is a slight male predominance.[7] These tumors are mainly sporadic,[3] although familial forms with autosomal dominant inheritance have been documented.[3,7]

GISTs are associated with a number of symptoms including GI bleeding, obstruction, perforation, dysphagia, pain, or an abdominal mass, depending on their location. Preoperative diagnosis is difficult as imaging is heterogeneous with nonspecific features. It occurs in patients at the sixth decade of life and can arise anywhere in the GI tract from the esophagus to the rectum. GISTs (mainly tumors larger than 4 cm) may present as abdominal emergencies, including GI hemorrhage, usually due to pressure necrosis and ulceration of the overlying mucosa, intestinal obstruction, or perforation. Perforations are more common

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for GISTs of the small bowel compared to other anatomical sites.[8]

CASE REPORTS

Case 1

A 49-year-old female with skin lesions of neurofibromatosis, presented to the acute internal medicine department with melena, loose stools, and mild abdominal pain, for more than 6 months. The initial blood tests revealed severe anemia with hemoglobin at 4.6 g/dL, with low mean corpuscular volume (MCV) and low ferritin, 74 and 10, respectively. After having 2 units of packed red blood cell (PRBC)(blood transfusion), she was investigated with gastroscopy and colonoscopy, and both tests were reported to be normal. Then, we proceeded with contrast enhanced CT scan abdomen and pelvis, to find the cause of her anemia. The CT scan has revealed a small-bowel lesion with necrotic areas and multiple calcifications [Figure 1a and b]. The radiologist proposed a differential diagnosis of small-bowel hemangioma, carcinoid, and small-bowel GIST. After due consenting, the patient had laparoscopic assisted small-bowel resection and end-to-end hand-sewn anastomosis. The patient had not needed further blood transfusions and had improved with iron supplementation. Patient was discharged on the 4th postoperative day, and her hemoglobin on the 7th postoperative day was 9.6 g/dL, and had no melena after the surgery. Histopathology was reported to be spindle cell type of GIST-Unifocal 3.5 cm × 2.8 cm × 2.6 cm neoplasm. Low grade <5 mitosis/50 high power field (HPF), necrosis was present; and all margins-free of a tumor, with distance from closest margin-1.5 cm from one cut margin [Figure 2a]. The margins are free of tumor-adjacent mucosa shows ulceration with granulation tissue with occasional mitosis noted. Further immunohistochemistry (IHC) showed positive CD117 and CD34 and a negative S-100, confirming the diagnosis of small-bowel gastrointestinal stromal tumor [Figure 2b]. The case was discussed in tumor board and in view of low-grade tumor, only routine follow-up was recommended. Patient was followed up after 4 weeks, and was noted to have a hemoglobin of 11.6 with near normal MCV, and had good weight gain and improving appetite.

Case 2

A 66-year-old female presented to the internal medicine department with chronic anemia and a history of melena with abdominal bloating for 6 months with a background history of hypothyroidism. Routine initial investigations confirmed microcytic anemia with hemoglobin at 6.3 g/dL, and MCV of 76. The patient underwent endoscopic investigations, and both gastroscopy and colonoscopy were reported to be normal. This led to a contrast-enhanced CT scan of the abdomen and pelvis, which showed a lesion in the proximal jejunum, about 15 cm from the duodenal-jejunal junction [Figure 3a and b]. Preoperatively, the patient had 2 units (PRBC) blood transfusion, and after due consenting, she had laparoscopy-assisted small-bowel resections and handsewn end-to-end anastomosis [Figure 4b]. Postoperative recovery was uneventful and the patient was discharged on 4th postoperative day. Histopathology reported the lesion to be a spindle cell type of small-bowel GIST-gastrointestinal stromal tumor-a submucosal nodule measuring 1.8 cm × 1.7 cm × 1.6 cm, mitosis <1/5 mm^2, histologic grade-G1; necrosis-not identified,

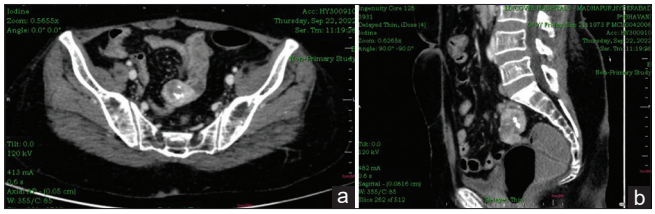

Figure 1: (a and b) Coronal and sagittal sections showing calcifications in the small-bowel lesion

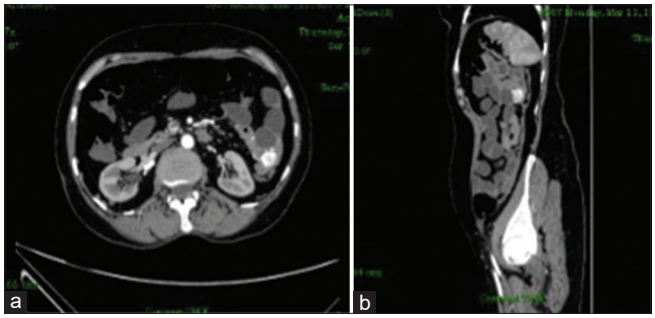

Figure 3: (a and b) CT images, coronal and sagittal views of jejunal lesion

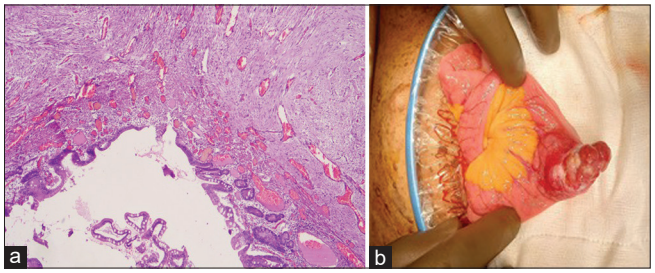

Figure 2: (a and b) Histopathology of case 1 showing ulcerated mucosa with spindle cells and intraoperative picture

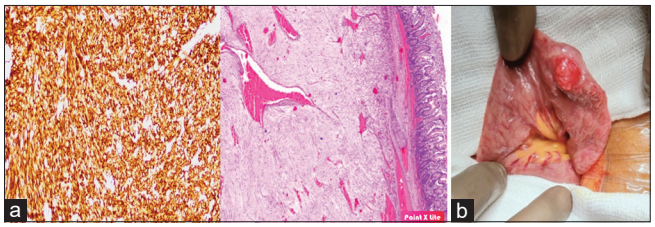

Figure 4: (a and b) CD117/DOG1 staining, H and E staining of gastrointestinal stromal tumor lesion and intraoperative picture

proximal, and distal resected margin-free of a tumor with cut margin away at 4 cm [Figure 4a]. Further, IHC showed CD117 C KIT positive, DOG1 EP332 Positive, and CD34 QBend10 Positive, supporting the diagnosis of small-bowel GIST. In view of the low-risk features, the tumor board proposed routine follow-up. After 6 weeks, her hemoglobin and MCV returned to normal at 12.5 g/dL and 86, respectively.

DISCUSSION

The most common site for GIST is the stomach (60%–70%), followed by the small bowel (25%–35%).[9] GISTs involving the esophagus, appendix, colon, and rectum are rare, and tumors arising from the omentum, mesentery, or retroperitoneum have been documented; but most of these were found to be metastatic from gastric or intestinal primaries.[7] Small intestinal GISTs require a special and individualized diagnosis and treatment, given their heterogeneity. The small intestine, which comprises most of the GI tract, is considered to be a relatively specialized organ. Because small intestinal neoplasms are usually rare, they are difficult to detect in early images. As a result, they are often overlooked and delayed in diagnosis.[10,11] GISTs of the small intestine are currently considered more invasive than GISTs of the same size in the stomach, and their incidence has been rising in the past few years, due to advances in radiology and endoscopy techniques, as well as improved physician awareness. Small intestine GISTs predominantly affect people from 40 to 70 years of age.[12] Jejunal GISTs, which comprise 10% of all GISTs,[3] are usually symptomatic and patients suffer from abdominal pain and early satiety. They may also have symptoms secondary to obstruction or hemorrhage. Perforation with acute diffuse peritonitis is rare.[4,13,14] Due to the nonspecific symptoms and signs, it is difficult to diagnose jejunal GIST preoperatively. Although specific signs and symptoms are absent,[15] most GISTs (70%) are symptomatic, mainly presenting with vague abdominal pain.[5] Other symptoms include nausea, vomiting, early satiety, and abdominal fullness. The remaining (30%) are asymptomatic and diagnosed incidentally. These latter tumors are usually small-sized tumors (<2 cm).[3,9,16]

GISTs result from incidental neoplastic disease usually found with nonspecific clinical manifestations.[12] These clinical manifestations are primarily associated with the tumor diameter, the presence or absence of tumor cracks, and the tumor's relationship with surrounding tissues, which cause symptoms such as abdominal pain, abdominal mass, and bleeding.[17] Other symptoms include abdominal distention and fullness, early abdominal distension, nausea, vomiting, and palpable swelling or pain.[18]

If there are symptoms, the most common symptom will be GI bleeding, such as hematemesis or anemia, which can also cause intestinal obstruction or even perforation.[19] Intraperitoneal hemorrhage is often caused by necrosis and ulceration.

The frequency of small intestine GISTs is slightly below that of gastric GISTs, whereas the major emergency manifestation of GISTs of the small intestine is intestinal obstruction.[20] It has been reported in the literature that intussusception caused by small intestine GISTs is quite rare in adults, a few cases of GISTs of the small intestine with hepatic abscess have been reported. Rodrigues *et al*.[11] reported a case of small intestine GISTs with suppurative liver abscess, suggesting that differential diagnosis of abscess and liver metastasis in small intestine GIST patients is needed. The diagnosis of neoplasms of the small intestine is a continuous challenge that is often neglected clinically, characterized by low morbidity, common clinical symptoms, wide imaging manifestations, pleomorphic bowel, and overlapping of intestinal loops. The diagnosis of small intestinal GISTs is a crucial task for clinicians. Clinical history, endoscopic examinations, and imaging examinations can greatly benefit diagnosis.

CONCLUSION

Although endoscopic investigations (gastroscopy and colonoscopy) are part of standard protocols in the evaluation of microcytic anemia, an contrast-enhanced CT scan is useful in patients who may be unfit and may not prefer to have invasive endoscopic investigations. As evident by our two case scenarios, a contrast-enhanced computed tomography (CT) scan is a valuable investigation and should be considered in the evaluation of anemia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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Case Report

Role of microsurgery and free tissue transfer in reconstruction of complex defects of head and neck postablative procedure for cancer

ABSTRACT

The field of reconstructive microsurgery has witnessed considerable advancements over the years, driven by improvements in technology, imaging, surgical instruments, increased understanding of perforator anatomy, and experience with microsurgery. In the case discussed, free fibula flap is used to reconstruct the mandible and soft tissue defect and giving a near-normal life cosmetically and functionally.

Keywords: Mandibulectomy, microsurgery, squamous cell carcinoma

INTRODUCTION

Squamous cell carcinoma (SCC) involving the lower buccal mucosa and mandible presents a challenging clinical scenario characterized by malignancy in the oral cavity's intricate structures. Often associated with risk factors such as tobacco use and alcohol consumption, this condition manifests through nonhealing ulcers or lesions.[1] Diagnosis involves a thorough evaluation, utilizing imaging, and biopsy techniques. The complex nature of the disease necessitates a multidisciplinary approach, with surgical teams often performing wide local excision and hemimandibulectomy, as exemplified in the case discussed. Reconstruction, such as free fibula osteocutaneous flap cover, plays a crucial role in restoring form and function.[2] The successful management of this condition requires early detection, advanced surgical techniques, and ongoing research for improved therapeutic outcomes.

CASE REPORT

A 59-year-old male presented with a 6-month history of a nonhealing ulcer in the lower gingivobuccal sulcus. Upon investigation, the diagnosis revealed SCC of the lower buccal mucosa infiltrating the mandible. In response, a comprehensive approach was adopted, with a surgical oncology team performing a wide local excision, accompanied by class IV hemimandibulectomy and neck dissection.

The surgical procedure involved meticulous planning and execution. The reconstruction of the mandible and floor of the mouth was undertaken using a free fibula osteocutaneous flap cover. The intricate process included multiple osteotomies, addressing the class IV hemimandible by reconstructing the condyle, ramus, body, symphysis, and a portion of the mandible on the opposite side. The fibula bone, along with its accompanying skin paddle, played a crucial role in restoring both the structural and surface elements of the affected areas [Figure 1].

Remarkably, the surgery proceeded without any postoperative complications, reflecting the skill and precision of the surgical

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Figure 1: (a) Class IV hemimandibulectomy defect, (b and c) Free fibula flap design, (d-f) Fibula bone with skin paddle with osteotomy, (g) Free fibula flap designed into mandible shape, (h) Mandible reconstructed and anastomosis done with facial artery and vein, (i) X-ray showing the reconstructed mandible

team. Postoperatively, the patient's recovery was notable, marked by the initiation of oral feeds from postoperative Day 4. In addition, by postoperative Day 3, the patient demonstrated early ambulation, supported by a splint.

DISCUSSION

Cancer of the oral cavity involving bone requires segmental mandibulectomy to ensure adequate ablation. Margins must be adequate, or local recurrence of the tumor is inevitable.[3] Mandibulectomy can be used in various settings, including infectious etiologies (osteomyelitis), osteoradionecrosis or a benign (e.g., ameloblastoma), or malignant neoplastic process (e.g., invasive SCC) that involves the jaw.[2] In cases of severe oral and maxillofacial trauma, if a section of the mandible is not salvageable, mandibulectomy may be an appropriate treatment. Segmental mandibular resection is the most important decision to be made in the management of oral cancer. Reconstruction is more difficult and more essential for functional and esthetic outcomes in cases that need large defects to treat them.[4] Malignancy or in those cases that include the condyle. Dysphasia is an important postoperative problem in patients undergoing mandibulectomy. Mandibulectomy causes limitation of lip and jaw movements and subsequent slowing of the oral stage of swallowing. The vascularized fibular free flap would be the gold standard for mandibular reconstruction. It has the advantage of providing, in addition to the bone graft, soft tissue, particularly muscle and skin (osteocutaneous and osteomyelitis cutaneous flap).

CONCLUSION

This case exemplifies the successful integration of surgical expertise, utilizing advanced techniques such as free fibula osteocutaneous flap cover, to address a challenging presentation of SCC involving the lower buccal mucosa and mandible. The patient's positive response to the treatment and early recovery milestones underscore the effectiveness of the chosen surgical intervention and the comprehensive care provided by the medical team. Regular follow-up and continued monitoring will be essential to track the patient's long-term progress and ensure sustained positive outcomes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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There are no conflicts of interest.

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Case Report

May–Thurner syndrome

ABSTRACT

A 37-year-old female with a history of severe adenomyosis and endometriosis presented with left leg swelling and pain. She was found to have a deep vein thrombosis in her left leg and underwent treatment to remove the clot. Due to her complex medical history, she will be monitored closely and may need further treatment to prevent future clotting.

Keywords: Follicles, leiomyoma, May–Thurner syndrome, thromboembolism

INTRODUCTION

May Thurner syndrome which is also known as Cockett syndrome or Iliac vein compression syndrome is a rare disorder, in which the right iliac artery compresses the left iliac vein leading to deep vein thrombosis (DVT) in the left lower limb. Females are affected more commonly between 20 s and 40s.[1,2] Females with uterine leiomyoma, adenomyosis, arteriovenous (A-V), and postpartum women are more predisposed to develop this condition.[3] Females with May–Thurner are believed to have pelvic congestion leading to chronic pelvic pain. Till date, no case of May–Thurner with adenomyosis has been reported.

CASE REPORT

A 37-year-old female, with a known case of endometriosis and adenomyosis, presented to the emergency room (ER) with complaints of left lower limb swelling for 7 days, progressive from legs to thighs, and associated with pain for 2 days. She had a history of shortness of breath (SOB) on exertion. She was diagnosed with severe adenomyosis with uterine size reaching up to 16 weeks of gestational uterus (16 cm). She had undergone surgery for adenomyosis previously and the surgical diagnosis was grade IV endometriosis with frozen pelvis and adenomyosis. Two weeks before the presentation, she had undergone an oocyte retrieval procedure. However, oocytes were retrieved abdominally from only the right side. The left ovary did not grow any follicles. The patient was admitted and a diagnostic workup including color Doppler of both lower limbs was done, which showed left lower limb DVT extending from the superficial femoral vein into popliteal veins, thrombosis of the proximal great saphenous vein. The patient underwent mechanical thrombectomy plus intravascular ultrasound (IVUS)-guided venoplasty with 12-mm and 8-mm balloons.

IVUS revealed two tandem stenosis at the left common iliac vein stenosis at the inferior vena cava (IVC) junction and left common femoral vein stenosis before the origin of the left internal iliac vein [Figure 1]. The patient was kept under the observation of cardiologists and treated with anticoagulants and antiplatelets, and conservative measures were taken for DVT. As there is a risk of recurrence, she had been advised for stenting in the future.

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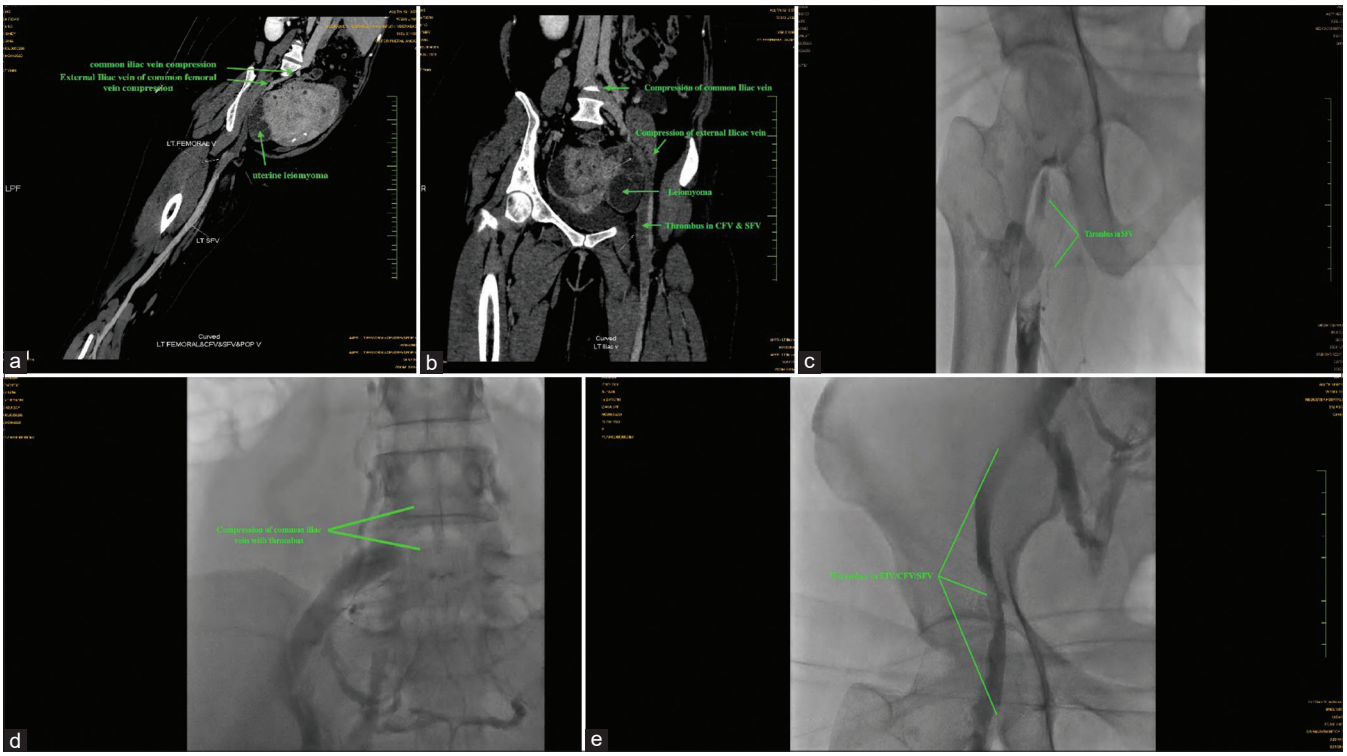

Figure 1: (a) CT Venogram: Compression of External Iliac vein and common femoral vein by uterine Leiomyoma and compression of common iliac vein narrowing. (b) CT Venogram: Compression of External Iliac Vein, Common femoral vein with Thrombus in Common femoral vein, Superficial vein, Common Iliac vein. (c) Peripheral venogram: Showing thrombus in Superficial femoral vein. (d) Peripheral venogram Showing compression of the common iliac vein with thrombus. (e) Peripheral venogram Showing thrombus in External Iliac vein, Common femoral vein, Superficial femoral vein

DISCUSSION

May–Thurner is an underdiagnosed condition. Only 2%–5% of patients undergoing lower limb evaluation for venous disorders are diagnosed with May–Thurner syndrome.[4] It is caused by compression of the left common iliac vein by the right iliac artery against the fifth lumbar vertebra, more so common in vascular malformations [Figure 2]. Many patients have no symptoms and quite a few are diagnosed postmortem. The overlying artery induces compression on the left common iliac vein by its anatomical position and chronic pulsatile force causes intimal hypertrophy resulting in narrowing of the veins.[5] This obstruction causes venous stasis causing leg swelling, varicose veins, chronic venous stasis ulcers, iliofemoral DVT, and complications such as pulmonary thromboembolism (PTE) and postthrombotic syndrome (PTS).[4-6] Predisposing factors include dehydration, prolonged immobilization, contraceptive therapy, and major surgeries. The common reasons in females are gravid or enlarged uterus such as adenomyotic or fibroid uterus.[5] It may also present in some women with pelvic kidney, renal transplantation on the left side, spinal abnormalities, and adnexal masses extending to the lateral pelvic wall. Here, in this case, an adenomyotic uterus was found to be the reason behind the DVT. People with May–Thurner are usually

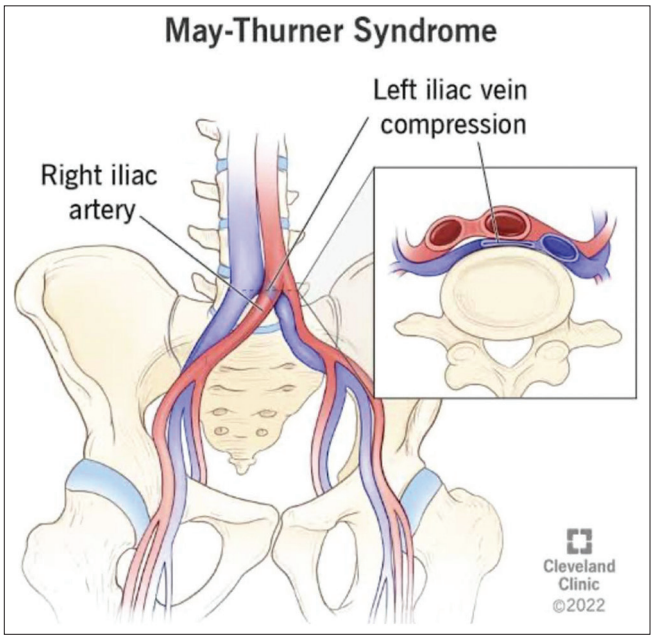

Figure 2: May-Thurner syndrome

asymptomatic unless they develop DVT which is unilateral and mostly in the left lower limb. Diagnosis can be made by noninvasive imaging modalities by color Doppler study of lower limbs, computed tomography venography, and magnetic resonance venography. IVUS and catheter-based

venograms form the invasive imaging modalities. Venogram versus IVUS for diagnosing iliofemoral vein obstruction clinical trial showed IVUS has more sensitivity in characterizing iliac vein lesions and helps in guiding treatment, hence improving outcomes. IVUS provides crucial information in treating DVT, including lumen and vessel diameter, location and nature of thrombus, confirmation of proper vessel selection, and proper deployment of stents.[6] A high degree of suspicion is needed in cases predisposed to this condition as early detection and immediate treatment can prevent the catastrophic pulmonary thromboembolic event.

Treatment options include angioplasty and stenting, division of the right common iliac artery, and relocation behind the left common iliac vein or IVC. In some cases, a contralateral saphenous vein graft bypasses to the ipsilateral common femoral vein with the creation of a temporary arteriovenous fistula (Palma crossover) was done.[7,8] The reported long-term success, primarily defined as patency of the left common iliac vein or vein bypass is 40%–80%.[8] Patients with iliofemoral thrombosis have a high risk of recurrence and complications such as PTS despite anticoagulation.[6] Hence, percutaneous mechanical thrombectomy with stenting has been advised as it allows the removal of all types of clots subacute and chronic, and the risk of recurrence is reduced with stenting. After the intervention, effective anticoagulation therapy and good patient follow-up are essential to prevent recurrence and PTS.[6] The cause triggering the compression should be treated to avoid recurrence.

CONCLUSION

May–Thurner is an underdiagnosed condition. However, higher suspicion in predisposed cases is needed for early diagnosis and management. With the increased incidence of adenomyosis and deep infiltrating endometriosis, these cases are on suspected rise. Proper surgical and medical management is the key to prevent PTE.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Cardiac amyloidosis – A rarely acknowledged cause of heart failure: A case report and review of literature

ABSTRACT

Amyloidosis is characterized by the precipitation of insoluble, misfolded, fibrillary proteins in the extracellular matrix in the form of beta-pleated sheets, leading to the loss of normal tissue architecture and ultimately organ dysfunction. The manifestations of the disease are due to the noxious effects of aggregated proteins (Amyloid) deposited in the tissues. Amyloidosis involves multiple organs, including the heart, kidneys, liver, soft tissues, peripheral and/or autonomic nervous system, and gastrointestinal tract. Cardiac amyloidosis is one of the myriad manifestations of systemic amyloidosis. It is characterized by extracellular deposition of amyloid fibrils, leading to progressive cardiac failure. We report a case of a 54-year-old male, who presented to us with a history of exertional dyspnea for the past 2 years with left ventricular systolic and diastolic dysfunction unexplained by the coronary anatomy. The findings on cardiac imaging led us to the suspicion of cardiac amyloidosis. Further, evaluation with an abdominal fat pad and rectal mucosal biopsy confirmed amyloidosis.

Keywords: Amyloidosis, cardiac failure, coronary imaging

INTRODUCTION

Amyloidosis is a multisystem disorder characterized by the precipitation of insoluble, misfolded, fibrillary proteins in the extracellular matrix in the form of beta-pleated sheets, leading to the loss of normal tissue architecture and ultimately organ dysfunction.[1] The affected organs include the heart, kidneys, liver, soft tissues, peripheral and/or autonomic nervous system, and gastrointestinal tract. Based on the type of amyloid protein, it may be systemic or localized.[2] Although cardiac involvement is frequently seen in up to 50% of systemic primary amyloidosis, isolated cardiac amyloidosis is infrequent, and in these cases, the diagnosis may be a miss due to minimal or absent extracardiac features. Cardiac amyloidosis is characterized by extracellular deposition of amyloid fibrils, leading to progressive heart failure often associated with a significant morbidity and mortality. Associated delay in diagnosis leads to advanced stages of heart failure.[3] Characteristic findings of cardiac amyloidosis on electrocardiogram (EKG), echocardiogram, and cardiac magnetic resonance (CMR) imaging may help in reaching the diagnosis. The gold standard for diagnosing cardiac amyloidosis is endomyocardial biopsy. Since it is more invasive, an abdominal fat pad biopsy is preferred over endomyocardial biopsy to signify a conclusive diagnosis of systemic amyloidosis.[4] We present a case of primary systemic amyloidosis-amyloid light chain (AL) type with predominant features of cardiac involvement.

CASE REPORT

A 54-year-old male with a history of type 2 diabetes mellitus for 11 years presented to us with progressive breathlessness

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on exertion, paresthesia's of the upper limb, decreased appetite, and weight loss over the last 2 years. He denied any history of smoking or alcohol/drug abuse. His physical examination showed a pulse rate of 82 beats/min, blood pressure of 100/70 mmHg, normal jugular venous pulse, and normal heart and lung on auscultation. Twelve-lead EKG revealed poor R-wave progression with a pseudoinfarction pattern [Figure 1a] and transthoracic echocardiogram showed increased global left ventricular (LV) thickness with a mild increase in echogenicity, biatrial enlargement, mild global hypokinesia, moderate LV systolic dysfunction, and Grade III diastolic dysfunction [Figure 1b]. Speckle tracking with global strain revealed reduced global strain with apical sparing [Figure 1c].

Laboratory testing was significant for N-terminal pro b-type natriuretic peptide elevation at 2149 pg/mL (Normal <125 pg/mL), troponin I: 0.02 (0–0.12 ng/mL). Diagnostic angiography revealed no significant epicardial coronary artery disease. He was initiated on Guideline Directed Medical Therapy for heart failure despite which the patient continued to show Class II New York Heart Association (NYHA) symptoms. Follow-up ECG showed frequent premature ventricular complexes (PVC's). Five-day Holter was done, which showed frequent PVCs with a burden of 13.9% and occasional nonsustained ventricular tachycardia's. Beta blocker dose was increased, but the patient could not tolerate because of symptomatic hypotension, hence beta blockers were down-titrated and initiated on oral amiodarone. Cardiac magnetic resonance imaging done showed extensive transmural enhancement of myocardium at mid and apical segments of left ventricle, basal anteroseptal, inferior, and inferolateral segments, subendocardial enhancement at basal anterolateral and inferoseptal segments suggesting the possibility of diffuse infiltration of myocardium. The percentage of enhanced myocardial volume was 71% which was disproportionate to the amount of LV systolic dysfunction leading us to suspect cardiac amyloidosis [Figure 2a and b]. A hematologist consult was sought for and a complete evaluation for systemic amyloidosis was worked up. Relevant laboratory findings are summarized in Table 1 and Figure 2c.

His serum protein electrophoresis was negative for M-band. Immunofixation did not show, and heavy or light chain restriction, light chain ratio was deranged. Bence–Jones protein was not detected in the urine. Bone marrow aspirate and biopsy showed erythroid prominence with 10%–15% plasmacytosis, the plasma cells are CD138 positive, and the Lambda light chain is restricted. A bone tracer cardiac scintigraphy using ^{99m}technetium (Tc)-labeled pyrophosphate (PYP) was done which showed a heart-to-contralateral ratio of 1.44 [Figure 3a] making a diagnosis of transthyretin (TTR)-related cardiac amyloidosis less likely. With the above findings, a decision

Table 1: Serum protein electrophoresis (SPEP)

Parameters	Laboratory values with reference ranges
Total protein	6.6 g/dL (6.0–8.3 g/dL)
Albumin	3.8 g/dL (3.6–5.4 g/dL)
α1 globulin	0.4 g/dL (0.2–0.4 g/dL)
α2 globulin	1.0 g/dL (0.5–1.0 g/dL)
β1 globulin	0.4 g/dL (0.3–0.6 g/dL)
β2 globulin	0.3 g/dL (0.2–0.5 g/dL)
γ globulin	0.8 g/dL (0.7–1.5 g/dL)
Albumin, globulin ratio	1.3 (1.1–2.2)
β2 microglobulin	4.4 mg/L (0.81–2.19 mg/L)
Serum immunofixation electrophoresis	Nonsignificant levels of IgA, IgG, IgM IgA total: 123.2 (70–400 mg/dL) IgM total: 263.3 (40–230 mg/dL) IgG total: 1840 (700–1600 mg/dL)
Serum free light chains	κ chain: 22.02 mg/L (3.3–19.4 mg/L) λ chain: 408.49 mg/L (5.71–26.3 mg/L) κ/λ ratio: 0.1 (0.26–1.65)
Serum protein electrophoresis	No M-band

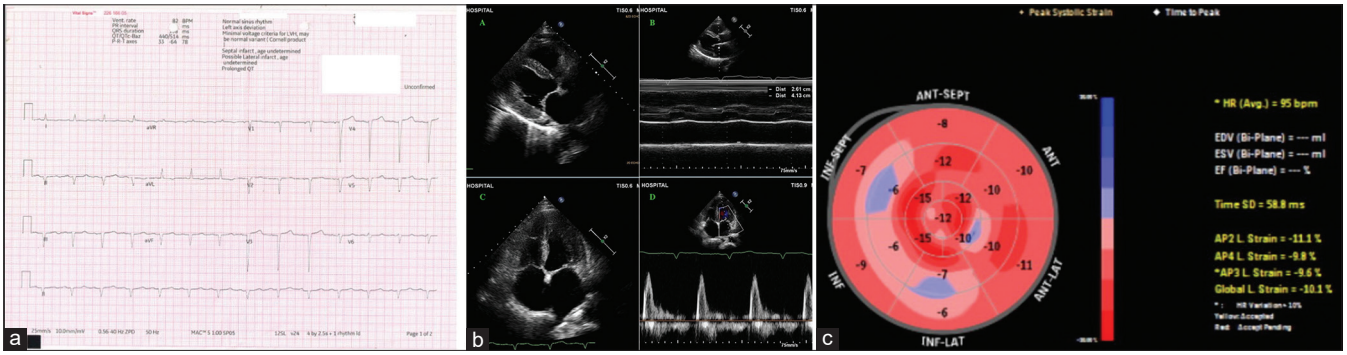

Figure 1: (a) A 12-lead electrocardiogram of our patient showing Q-waves in anterior leads due to myocardial fibrosis, giving a pseudoinfarction pattern. (b) Transthoracic echocardiogram showing: (a) Increased left ventricular thickness with a mild increase in echogenicity, (b) Dilated left atrium on M mode, (c) Biatrial enlargement, (d) Mitral inflow gradient showing Grade III diastolic dysfunction (restrictive filling). (c) Speckle tracking with global strain revealed a reduced global strain of – 10.1% and relative apical sparing (RELAPS pattern)

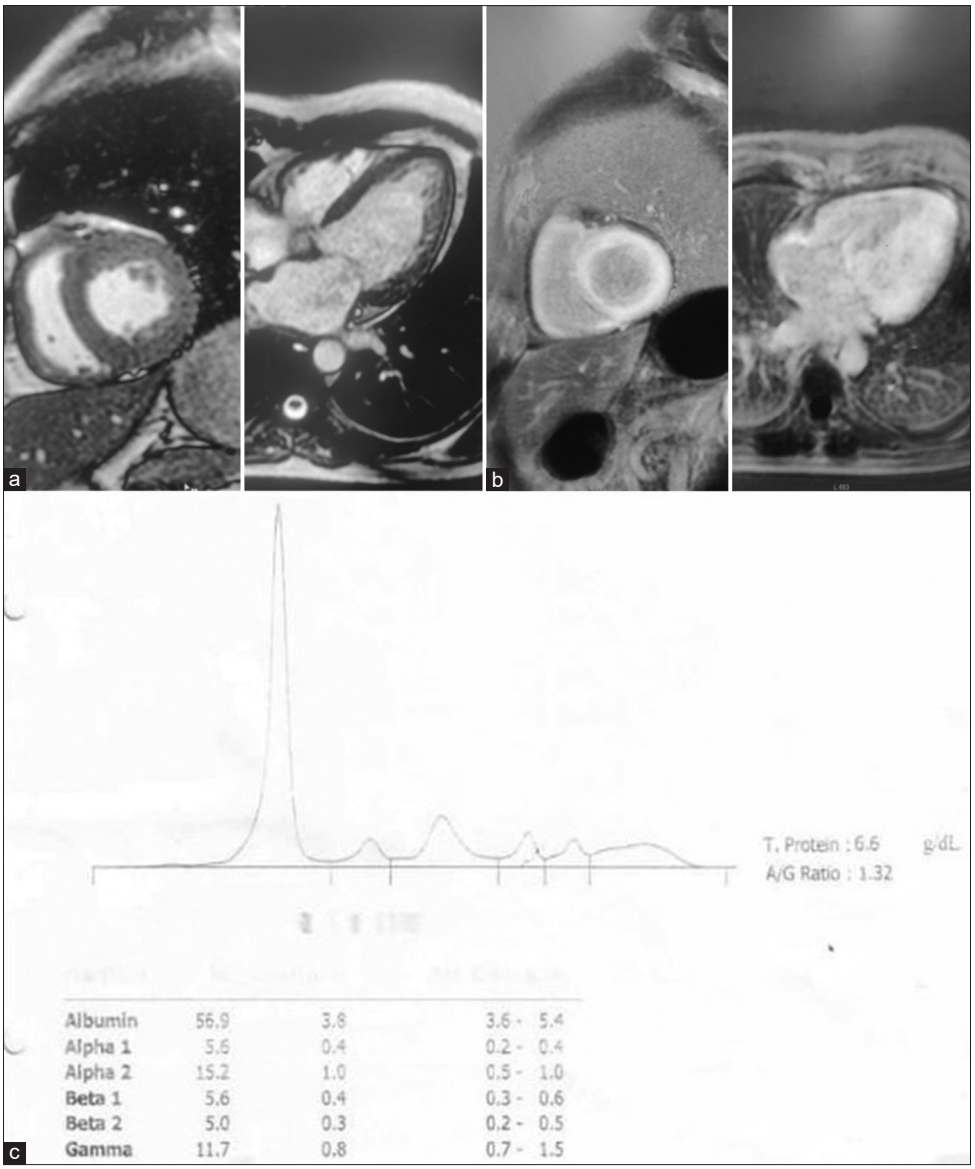

Figure 2: (a) Gradient echo sequences and steady-state free precession – White blood imaging shows the increased thickness of myocardium in all the segments of the left ventricle. Cine sequences show global left ventricular (LV) hypokinesia. (b) Postcontrast gradient sequence/basic fast field echo: Postgadolinium delayed enhancement study revealed diffuse transmural enhancement at basal, mid, and apical segments of LV. Sparing of a thin epicardial layer of myocardium at the basal anterolateral segment. (c) Normal pattern serum protein electrophoresis in our study

was made to perform an abdominal fat pad, and rectal mucosal biopsy for histopathological examination [Figure 3b] showed a congophilic material, lambda light chain restriction [Figure 3c], and apple-green birefringence under polarized light [Figure 3d]. After a review with the hematologist, he was commenced on a chemotherapy regimen with cyclophosphamide, bortezomib, and dexamethasone along with the continuation of heart failure drugs. Symptomatic improvement was noted during follow-up with better appetite, alleviation in a functional class of shortness of breath (SOB) from NYHA Class III to II, and improvement in palpitations. Laboratory values showed decreased serum-free light chains, predominantly λ post initiation of chemotherapy during follow-up [Table 2].

DISCUSSION

Cardiac amyloidosis is an infrequent diagnosis but should be considered in any individual with clinical features suggestive of heart failure due to restrictive physiology. Based on the type of amyloid protein, cardiac involvement in amyloidosis can be seen in the following five types: (A) AL or primary amyloidosis, (B) TTR or familial/hereditary amyloidosis, (C) systemic senile amyloidosis, (D) isolated atrial amyloidosis, and (E) serum amyloid A or secondary amyloidosis.[5] The diagnostic evaluation in suspected cardiac amyloidosis includes electrocardiography, echocardiography, CMR, serum protein electrophoresis, immunofixation, and free light chain ratio and in certain cases requires a endomyocardial

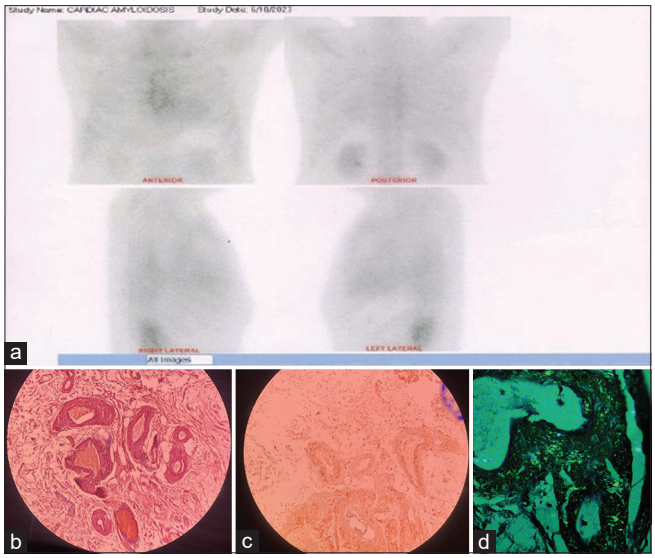

Figure 3: (a) Bone tracer cardiac scintigraphy using ^{99m}technetium-labeled pyrophosphate was done with a heart to contralateral ratio of 1.44 being obtained making a diagnosis of transthyretin-related cardiac amyloidosis less likely. (b) Histological Congo red staining imparting a hyaline pink appearance under light microscopy (Congo red stain x 400). (c) IHC shows lambda light chain restriction in the wall of the blood vessels as seen in the abdominal wall fat pad biopsy (×40; IHC lambda). (d) Apple-green birefringence in amyloid deposited areas of the blood vessel wall as seen under a polarized microscope (Congo red stain × 400)

Table 2: Serum free light chains post initiation of Chemotherapy

Test name	Result	Biological reference interval
Free κ light chain	12.31	3.3–19.4 mg/L
Free λ light chain	83.79	5.71–26.3 mg/L
κ/λ ratio	0.15	0.26–1.65

Table 3: Red flag or Clinical scenario in suspected Cardiac Amyloidosis

Heart failure
Aortic stenosis in individuals 65 years or older
Hypotension or normotensive if previously hypertensive
Sensory involvement
Autonomic dysfunction
Peripheral polyneuropathy
Proteinuria
Skin bruising
Bilateral carpal tunnel syndrome
Ruptured biceps tendon
Subendocardial/transmural late gadolinium enhancement
Reduced longitudinal strain with apical sparing
Decreased QRS voltage-to-mass ratio
Pseudo Q-waves on ECG
AV conduction disease
Possible family history

ECG: electrocardiogram, AV: Atrioventricular

biopsy. The most common findings in ECG are low precordial and limb-lead voltage and a pseudoinfarction pattern. Echocardiography usually reveals an increased left and right ventricle wall thickness with greater echogenicity (granular sparking) although it is not specific for cardiac amyloidosis. However, low voltage in ECG and interventricular septal thickness of >19.8 mm in echo, together, have a sensitivity of 72% and specificity of 91% for cardiac amyloidosis.[6] A high index of suspicion should be considered in individuals with LV wall thickness more than 12 mm with one or more than one red flag or clinical scenario included in Table 3.[7]

CMR gives better characterization of myocardial borders, myocardial wall thickness, and 3-dimensional images for ventricular volumes. However, the key finding in CMR that helps in the diagnosis of amyloidosis is disproportionate delayed gadolinium enhancement to systolic dysfunction. In amyloid heart, the distribution kinetics of gadolinium are altered due to extracellular deposition of amyloid, leading to retained contrast that produces the characteristic late gadolinium enhancement.[8] While abdominal fat pad biopsy may reveal the diagnosis in about 70% of patients, the gold standard for diagnosis remains the endomyocardial biopsy. Histological detection of amyloid deposits through Congo red stain and classic apple-green birefringence under polarized light confirms the diagnosis. Tc PYP uptake is seen with TTR amyloidosis but not with AL amyloid and can delineate the former from the latter[9] but is not a test used when there is high suspicion for AL amyloidosis.

Establishing an early diagnosis of amyloidosis is a challenge. Previous studies show that most patients require multiple physician visits and different medical specialists, often spanning >1 year, leading to a delayed diagnosis and advanced presentation of the organ system involved.[10]

Management of AL amyloidosis consists of medical optimization of the organs involved and chemotherapy to reduce the clonal plasma cell burden.

CONCLUSION

Although uncommon, amyloidosis is a multisystem infiltrate disorder that results in significant mortality and morbidity. Cardiac amyloidosis is invariably associated with worse outcomes. It requires a high level of suspicion based on the clinical setting, and the findings of noninvasive diagnostic workup. The most challenging issue is a significant delay in diagnosis, sometimes up to several years. Early suspicion and thorough investigation are critical to making a timely diagnosis and referral for treatment. A definitive diagnosis can only be made following a histological study. Our case highlights the multidisciplinary approach to early diagnosis and management for a better prognosis and patient care.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Lung wash in a struggle for breath – Pulmonary alveolar proteinosis

ABSTRACT

Pulmonary alveolar proteinosis (PAP) is an orphan disease characterized by the accumulation of lipoproteinaceous material in the alveoli due to macrophage dysfunction, leading to impaired gas exchange and hypoxemia of variable severity. Diagnosis is made by the constellation of clinical signs and radiological findings supported by bronchoalveolar lavage (BAL) or transbronchial lung biopsy reports. Whole lung lavage (WLL) is the treatment of choice. Here, we report a case of a middle-aged female diagnosed of having PAP based on BAL findings and treated with WLL.

Keywords: Autoimmune, connective tissue, pulmonary alveolar proteinosis, whole lung lavage

INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is an uncommon disease of variable clinical severity and characteristic radiological findings.[1] A crazy-paving pattern in computed tomography (CT) of the chest is suggestive of, but not specific, to PAP.[2] Sequential whole lung lavage (WLL) of the most affected lung is performed first to provide symptomatic benefit.

CASE REPORT

A 38-year-old female patient with no prior comorbidities presented to the emergency department with complaints of gradually progressive shortness of breath and dry cough for the past 1 month. There was no fever, weight loss, or any symptoms suggestive of connective tissue disorder. Initially admitted in another hospital for 3 days and treated with intravenous antibiotics with no significant clinical and radiological improvement. On presentation, she was afebrile with saturation of 96% on 4 liters of oxygen and pulse rate of 124 beats per minute. Respiratory system examination revealed bilateral lung crepitations. High-resolution CT (HRCT) of the chest revealed bilateral ground-glass opacities with septal thickening suggestive of "crazy-paving pattern" [Figure 1]. A possible diagnosis of PAP was kept, and she was evaluated for other causes. Her blood investigations were essentially normal except for elevated serum lactate dehydrogenase (LDH) levels (924 U/L). Bronchoalveolar lavage (BAL) was performed and milky fluid was obtained. Microscopic examination revealed eosinophilic material admixed with macrophages containing intracytoplasmic eosinophilic globules [Figure 2]. All cultures on BAL fluid were negative. Hence, a diagnosis of PAP was considered. Autoimmune workup was negative and anti-granulocyte-macrophage colony-stimulating factor (GM-CSF) antibody levels were not sent due to logistic issues. Multidisciplinary discussion (MDD) was done in our

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hospital and WLL was planned sequentially to clean the patient's lungs. WLL was done in operation theater with double-lumen tube (DLT) intubation and the left lung was cleaned first with 12 L of normal saline till clear lavage fluid was obtained [Figure 3]. The patient clinically and radiologically improved after the WLL. She was discharged in hemodynamically stable condition with a review after 2 weeks for WLL of the right lung.

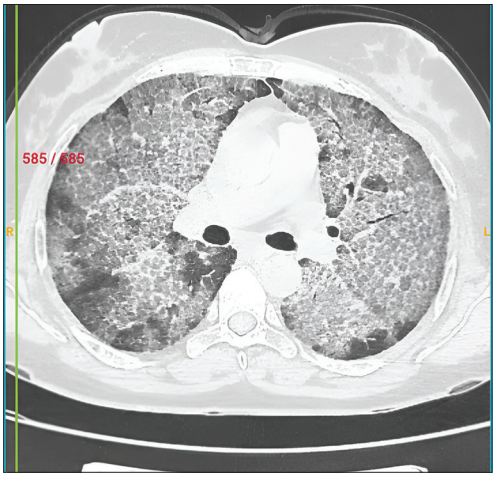

Figure 1: Computed tomography of the chest depicting "crazy-paving pattern"

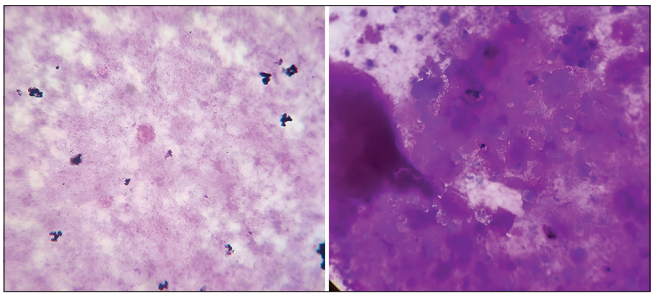

Figure 2: Periodic acid–Schiff staining of bronchoalveolar lavage fluid showing intracytoplasmic material in macrophages

Figure 3: Milky fluid collected after performing whole lung lavage

DISCUSSION

PAP is a rare disorder first described in 1958 by Rosen *et al*. and it is believed to be due to the defect in surfactant homeostasis.[3] This condition is characterized by dense accumulation of large amounts of a periodic acid–Schiff (PAS)-positive phospholipoproteinaceous material in the alveoli with preservation of lung interstitium. The pathogenesis is mainly attributed due to either diminished GM-CSF function or decreased number/impaired function of alveolar macrophages.[4] Clinically, three distinct forms of PAP exist: genetic, autoimmune (also called idiopathic or primary), and secondary.[5] Autoimmune PAP is the most common form (representing about 90% of all cases) and is characterized by circulating autoantibodies against GM-CSF in the patient's serum. The usual age of onset of PAP is in the third to fourth decade of life with male-to-female ratio of 3:1. Dyspnea and cough are the most common presenting symptoms. The physical examination is unremarkable, except for inspiratory crackles, cyanosis, and digital clubbing in less than 10% of cases.[6] HRCT of the chest shows patchy, ground-glass opacities with superimposed interlobular septal and intralobular thickening, a pattern commonly referred to as "crazy-paving pattern."[2] Routine investigations are usually normal except for elevated serum LDH. Measurement of serum anti-GM-CSF antibodies plays an important role in the diagnosis of autoimmune or primary PAP.[7]

Clinical and radiographic findings often suggest the diagnosis of PAP in suspected cases, while findings on examination of a BAL fluid or lung biopsy can establish the diagnosis.[8] The lavage fluid in patients with this disorder has an opaque, milky appearance. It contains large and foamy alveolar macrophages and increased numbers of lymphocytes. Lung biopsy specimen reveals an accumulation of PAS-positive material in the alveoli with little or no inflammation.[9]

Management of PAP depends on the clinical status of the patient. Asymptomatic patients may be closely observed and monitored without specific treatment. For symptomatic patients, WLL is the most effective form of treatment and, for a long time, considered the "standard of care."[10] Multiple reports suggest that performing WLL significantly improves the 5-year survival rate in PAP patients. While performing WLL, usually the most radiologically affected lung is lavaged first using DLT, followed by the other lung after 2–3 weeks. There is significant clinical and radiological improvement after performing WLL. Currently, no drug is approved for the treatment of PAP but given the role of anti-GM-CSF autoantibodies in the pathogenesis of autoimmune PAP patients some people tried using GM-CSF with modest

clinical benefits.[11] Nevertheless, this approach is not widely available and less effective than WLL when used as monotherapy. Additional therapies such as rituximab and plasma exchange have been employed in individual patients who did not respond or were intolerant to WLL.[12,13] Lung transplant is reserved for selected patients with severe refractory PAP, although PAP sometimes recurs in the allograft.[14]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

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Case Report

An atypical rare neurologic complication of histiocytic necrotizing lymphadenitis (Kikuchi–Fujimoto Disease)

ABSTRACT

Kikuchi–Fujimoto disease (KFD), also known as histiocytic necrotizing lymphadenitis, is a rare disease first reported in 1972 by Kikuchi and Fujimoto *et al*. It is more common in young females under 30 years of age. It is a self-limited disease characterized by cervical lymphadenopathy. Headache accompanied by fever is a common symptom of this disease; however, the central nervous system (CNS) can also be involved. CNS involvement in KFD is extremely rare and remains a diagnostic challenge. We describe a KFD patient with aseptic meningitis who had a headache as the first symptom of aseptic meningitis. Only 41 cases of aseptic meningitis associated with KFD have been reported worldwide, with just five cases (including our case) of KFD with meningitis as the first symptom. We report a case of KFD accompanied by aseptic meningitis with leptomeningeal enhancement.

Keywords: Aseptic meningitis, histiocytic necrotizing lymphadenitis, Kikuchi–Fujimoto disease, lymphadenopathy

INTRODUCTION

Histiocytic necrotic lymphadenitis, first described by Japanese pathologists Kikuchi and Fujimoto *et al*.[1,2] and also called Kikuchi–Fujimoto disease (KFD), is a rare local lymphadenopathy with a benign course and with clinical manifestations including fever, lymphadenopathy, rash, hepatosplenomegaly, central nervous system (CNS) symptoms, and hemophilic cell syndrome. KFD involves a variety of tissues and organs as well as the CNS causing damage to the meninges, brain parenchyma, and peripheral nerves and even presenting neurological symptoms as prominent clinical manifestations or first symptoms. To date, most reports are based on the pathological features of KFD, and clinical reports of neurological damage as the first symptom are rare. Herein, we discuss the case of a patient diagnosed with aseptic meningitis as the first clinical feature and who was ultimately diagnosed with KFD.

CASE REPORT

Informed consent was taken prior from the patient. A 31-year-old married female came with a complaint of headache for 5 days. She had a single episode of fever, which was subsided, but headache persisted, hence admitted to our hospital. She had no significant past medical history. There was no history of rash, joint pain, arthritis, and fatigue. There was no history of night sweats and diarrhea., Her family history was unremarkable. The temperature on admission was 99.2°F. On systemic examination, neurological

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examination revealed meningeal irritation signs, including neck stiffness and Kernig's sign, were absent. No other abnormality was detected on neurological examination. No significant abnormality was detected on other systemic examination. On admission, the laboratory test results revealed a normal complete blood count except mild leucopenia with a total WBC count of 3300 per cu mm with normal differential count. Erythrocyte sedimentation rate was slightly raised by 58 mm h.

Coagulation tests, procalcitonin, C-reactive protein, antistreptolysin O, rheumatoid factor, and tumor markers are normal magnetic resonance imaging (MRI) brain, suggestive of axial T1 and coronal fluid-attenuated inversion recovery (FLAIR) postcontrast images showing leptomeningeal enhancement in bilateral posterior temporal and parieto-occipital lobes [Figure 1a and b].

Cerebrospinal fluid (CSF) analysis revealed CSF protein slightly raised 76.7 mg/dl; rest all CSF glucose, Gram stain, ZN stain, and CSF for ADA were normal. On CSF fluid Microscopy, 10 cells were seen all were lymphocytes. Viral markers such as HIV, hepatitis B surface antigen, and hepatitis C virus done all were negative. Aseptic meningitis was suspected.

USG neck done suggestive of multiple left submandibular, jugular, and posterior cervical necrotic lymph nodes (LNs). Under local anesthesia strict aseptic precaution, fine-needle aspiration cytology (FNAC) from the left cervical LN was obtained. FNAC findings suggest lymphoproliferative disorder; however need clinical correlation and histopathological study for definitive diagnosis.

LN excision biopsy was done. Histological examination shows a partially effaced LN with preserved secondary follicles. These follicles show a central germinal center and preserved mantle zone. Few foci show spotty necrosis [Figure 2a]. Extensive apoptotic bodies and numerous histiocytes are seen with engulfed nuclear and necrotic debris. No well-formed granuloma was noted. By IHC, CD20 [Figure 2b] and CD3 [Figure 2c] highlight reactive B-cell and T-cells in the LNs, respectively. CD15 and CD30 highlight scattered reactive immunoblasts in the LNs. ALK 1 and EBV-LMP 1 are negative. Affected areas of the node predominantly show CD8-positive T-helper cells. MIB 1 is high in the germinal centers. Special stain AFB is negative for acid-fast bacilli. Findings favor KFD.

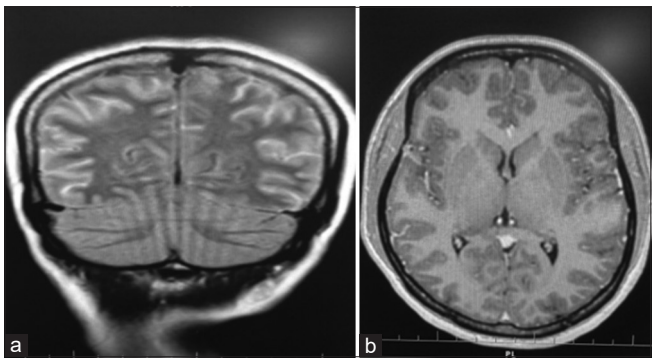

Figure 1: (a) Axial T1 fluid-attenuated inversion recovery (FLAIR) post contrast images showing leptomeningeal enhancement in bilateral posterior temporal and parieto-occipital lobes. (b) Coronal FLAIR post contrast images showing leptomeningeal enhancement in bilateral posterior temporal and parieto-occipital lobes

Positron emission tomography-computed tomography s/o increased standard uptake value in cervical LN. She was started on IV dexamethasone in view of persistent headache. She responded to dexamethasone. The patient's headache subsided. She improved and was later discharged on a tapering course of oral dexamethasone. The patient remained neurologically stable on follow-up.

DISCUSSION

KFD is primarily characterized by regional lymphadenopathy predominantly affecting adolescents.[3] In statistical terms, KFD is more common in young Asian women, with a peak age of onset between 25 and 29 years and a male-to-female ratio of 1:3–1:4.[4] In demographic terms, the distribution of KFD with meningitis has its own particular characteristics. Among the 41 cases of KFD with aseptic meningitis identified worldwide, the ethnic origins of the patients were European (5%), North American (7%), African (2%), and Asian (86%). Japan had the highest prevalence worldwide, accounting for 41% of cases. The average patient age was 22 years (80% of the patients were <30 years old), and the sex (male/female) ratio was 1.28:1. KFD is a self-limiting disease that usually resolves within 4–6 months. KFD has a reported recurrence rate of 3%–4% in adults.[5] Its etiology remains unknown. Various viruses, including CMV, EBV, parvovirus B19, and human herpesvirus 6, have been implicated as causative agents.[6]

Commonly, fever and regional lymphadenopathy are the main clinical manifestations of KFD. In addition, KFD can cause uveitis, subretinal macular infiltration, acute renal failure, hemophagocytosis syndrome, interstitial pulmonary disease, and other rare complications.[7] About 60%–90% of patients present with long-term fever of unknown cause and temperature fluctuations ranging from 38°C to 41°C. Posterior cervical lymphadenopathy is often the initial symptom, which is usually unilateral, accounting for 88.5% of cases.[3] Up to 40% of patients with KFD

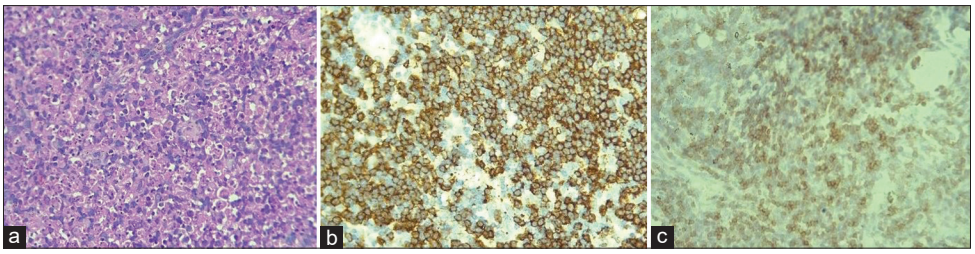

Figure 2: (a) Spotty necrosis in the lymph node. (b) CD20 - reactive B cells in the lymph node. (c) CD3 - reactive T cells in the lymph nodes

may present with nonspecific rashes, which may appear on the scalp, face, chest, back, and limbs, presenting with urticaria, rubella, erythema multiforme, papules, and papular abscesses.[8] The medical history, physical examinations, and medical imaging should be efficiently employed to rule out other forms of lymphadenitis. KFD mimics other common or more serious conditions, such as lymphoma or systemic lupus erythematosus (SLE); therefore, early and accurate diagnosis of KFD is crucial for avoiding unnecessary treatment. Cervical lymphadenopathy can also be the initial manifestation of SLE (12%–26%).[9] LN biopsy is the gold standard for the diagnosis of KFD, where in SLE usually presents with hematoxylin bodies and prominent plasma cells, which are rare in KFD.[10] In contrast to lymphoma, the affected LNs in KFD are solid, movable, and painful. Other laboratory tests and LN biopsy can rule out other diseases presenting as lymphadenopathy, such as SLE and NHL.

The clinical manifestations of KFD involving the CNS are complex and diverse, including meningitis, encephalitis, subdural effusion, optic neuritis, cerebellar ataxia, hemiplegia, and other signs.[11-15] KFD concomitant with neurological symptoms is rare and prone to missed diagnosis and misdiagnosis. Aseptic meningitis is the most common CNS complication of KFD, accounting for 2.8%–9.8% of KFD patients,[16] mainly manifesting as headache, vomiting, and convulsion. Meningitis usually occurs 2–3 weeks after lymphadenopathy, whereas meningitis as a first symptom of KFD is rare.[17] The course of KFD with aseptic meningitis usually takes 2–3 weeks, but a duration of 2–4 months has also been reported.[17] A meta-analysis of 244 patients with KFD showed that 4.5% (11 cases) were associated with neurological impairment, including aseptic meningitis (eight cases), polyneuritis, or acute cerebellar ataxia.[18] To date, of the 41 KFD patients with aseptic meningitis reported globally, 88% suffered headaches.

It is suggested that primary infection with unknown pathogens can produce causative substances, which may bind to target organs of the CNS. Avkan-Oguz *et al*.[19] reported a case of acute disseminated encephalomyelitis (ADEM) following KFD. Autoimmune response or immune reconstitution may result in concomitant KFD and ADEM. Byun *et al*.[20] found that the interval between the onset of lymphadenopathy and neurological symptoms was approximately 10–53 days. CSF test results of tuberculous meningitis are similar to those of KFD.[21] KFD may also exhibit symptoms of meningitis underscoring the importance of excluding bacterial and viral infections using CSF culture. T-spot examination and purified protein derivative also contribute to exclude tuberculosis infection. Guéguen *et al*.[21] found an increase in IFN-a levels in the CSF of patients with KFD without viral infection because of an upregulation of the IFN-a type I response. MRI findings, which include hyperintense T2 and FLAIR signals in the supratentorial white matter, deep gray matter, brain stem, cerebellum, temporal lobes, pons, and basal ganglia, can offer useful clues regarding CNS involvement.[22] An excisional biopsy can provide a critical clue to the diagnosis. Corticosteroids are the mainstay treatment for symptomatic KFD with encephalopathy. Cranial imaging after the initiation of corticosteroid therapy shows a reduction in the size and number of lesions.[23] According to Rezai *et al*.,[24] hydroxychloroquine has fewer adverse effects and is more efficacious than corticosteroids. The role of IVIG in KFD is for its anti-inflammatory effects for conditions where no autoantibody has been demonstrated.[17] Immunosuppressive therapy has also been recommended for complicated cases with increased LDH and raised serum antinuclear antibody titers to prevent fatal outcomes.[22] Excision of the affected LNs may also be therapeutic.[25] Glucocorticoids combined with IVIG can satisfactorily treat KFD complicated with hemophagocytic syndrome.[26]

A comparison table with KFD with encephalopathy in children published between 2010 and 2020 in PubMed with our case has been made[27] [Table 1].

CONCLUSION

KFD is a rare and benign disease that should be considered in patients presenting with fever and lymphadenopathy. Patients with KFD can develop neurological symptoms, such

TABLE 1: KFD with encephalopathy in children published between 2010 and 2020 in PubMed with current case

	Gender/ age	Neuroimaging findings	Interval between onset of lymphadenopathy and neurological manifestations	Neurological manifestations	Cerebrospinal fluid (CSF) analysis	Treatment	Outcome
Present case	F/31	leptomeningeal enhancement in bilateral posterior temporal and parieto-occipital lobes	5 days	Severe headache	Pleocytosis, high protein	IV DEX	good
Byun *et al*. [8]	M/12	Hyperintense signal in cerebellum and posterior aspect of bilateral occipital lobes	3 weeks	Severe headache, meningeal sign, seizure	Pleocytosis, high protein	IV Dex	Good
Jasti *et al*.[17]	F/15	hyperintense signal in dorsal midbrain and dorsal pons	2 weeks	Drowsy, nystagmus, blepharospasm	Pleocytosis, high protein	IV MP	good
Goncalves *et al*.[18]	M/9	Hyperintense signal in mesial temporal lobes, periaqueductal region, lateral wall of ventricle and mammillary bodies and perivascular enhancement	Around 26 days	Altered mentality	Pleocytosis, high protein	IV Dex	Neurocogni-tive sequelae
Huang *et al*.[19]	M/18	Leptomeninges thickened and enhancement	Simultaneously	Headache	Pleocytosis, high protein	IV Dex, oral MP and hydroxychl-oroquine	Good

as aseptic meningitis, multiple neuritis, or acute cerebellar ataxia. Conditions such as tuberculous meningitis, SLE, and infections should be excluded, and the possibility of encephalopathy-associated KFD should be considered. Therapy includes glucocorticoids combined with immunoglobulin. Antiviral therapy should be added if viral infections cannot be ruled out completely. Close follow-up is emphasized in these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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