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RESEARCH

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Evaluation of gastrointestinal complications in Egyptian patients after autologous stem cell transplantation using melphalan-based regimens

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Abstract

Background Autologous stem cell transplantation (ASCT) is a curative treatment for patients with hematological malignancies. Melphalan either alone or in combination with other chemotherapeutic agents is a widely used pre-transplant conditioning regimen with known gastrointestinal (GI) complications. We retrospectively evaluate the incidence and severity of GI toxicities, the possible risk factors, and their impact on transplant outcomes in 47 patients who received ASCT using melphalan-based conditioning.

Results Median age was 50 years. Among our patients, 48.9% received melphalan at 200 mg/m^2. Mucositis was developed in 93.6% of patients, nausea in 87.2% and grade 2 vomiting in 36.2% of patients. Grade 3 diarrhea was detected in 42.6%. Severe GI toxicities were associated with significantly delayed engraftment, longer hospital stay, and increased transfusion requirements but overall survival (OS) and transplant-related mortality (TRM) were not affected by the severity of GI symptoms.

Conclusion Despite using prophylactic and supportive care, some patients developed severe GI complications following different doses of melphalan with a negative effect on some transplant outcomes. Melphalan dose or disease type was not identified as a risk factor for severe GI toxicity. Additional larger prospective studies with higher doses, different formulations, and better prophylactic measures are warranted to evaluate potential risk factors and their impact on GI toxicities.

Keywords Autologous stem cell transplantation, Hematological malignancies, Melphalan, Gastrointestinal toxicity

Background

Over the past 2 decades, high-dose chemotherapy, followed by ASCT, remains the treatment of choice for patients with hematological malignancies such as multiple myeloma and refractory/relapsed lymphoma, leading to significant improvement in survival outcomes compared to the novel agents alone [1].

High-dose melphalan alone or in combination with other chemotherapeutic agents are the preferred conditioning regimens before ASCT in adult patients with multiple myeloma and lymphoma [2]. Melphalan is DNA alkylating agent with effective cytotoxic activity against

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clonal plasma cells and can also affect healthy progenitors causing a potential risk of early and late complications [3].

GI toxicity with different degrees of severity is the most common extramedullary complication of ASCT using melphalan-based regimens. These toxicities including oral mucositis, diarrhea, nausea, and vomiting, significantly impair the patient's quality of life, promote the development of infectious complications, and increase transplant-related morbidity and mortality [4].

Some studies had concerned with GI complications of ASCT using melphalan-based conditioning regimens, but the risk factors and the impact of melphalan dose on the severity of such toxicities are still not clear [5]. This study aimed to evaluate GI complications, the possible risk factors, and their impact on the outcome of ASCT using melphalan.

Methods

A single-center retrospective study was conducted on data obtained from an Egyptian BMT unit registry. We analyzed the medical records of all adult patients who received ASCT during the period from 2018 to 2022.

Patients aged 18 years or above at the time of first ASCT using melphalan-based conditioning were included. All patients had adequate performance status and negative serology for the hepatitis B virus and the human immune deficiency virus (HIV). Patients with inadequate clinical data or those with evidence of baseline GI problems were excluded.

Detailed history has been reviewed, including data about age, sex, performance status, associated comorbidities, viral status, CD34 cell dose, incidence and severity of infections and conditioning regimen-related GI toxicities, duration of hospital stay, engraftment and survival outcomes including OS and TRM at 100 days.

Conditioning regimens

Patients included in our study received melphalan in their conditioning regimens either at 200 mg/m^2 as the standard high dose melphalan for multiple myeloma or at 140 mg/m^2 as a combination with bendamustine/lomustine, etoposide, cytarabine, in either (BEAM) or (LEAM) regimens for lymphoma. Daily dose modification for all drugs according to renal and liver functions, when indicated.

Supportive care

All patients received anti-microbial prophylaxis consisting of levofloxacin, acyclovir, and fluconazole, and were upgraded when needed according to culture-based strategies. Pneumocystis jirovecii infection prophylaxis was done by trimethoprim-sulfamethoxazole (stopped on day 2 and re-initiated after engraftment).

All patients were examined for any oral or dental problems and treated before admission. Gastric protection by pantoprazole and anti-emetic prophylaxis was initiated according to the ematogenicity risk of the conditioning regimens and maximized as needed. We used ondansetron either alone or in combination with dexamethasone for anti-emetic prophylaxis for the majority of patients; aprepitant was used in some patients when available. All patients were encouraged for cryotherapy started 30 min before, during, and after the administration of melphalan as standard prophylaxis for oral mucositis.

During the transplant period, oral decontamination by nystatin and chlorohexidine mouthwash up to four times a day. Oral rinse with a solution containing (saline 0.9%, lidocaine, sodium bicarbonate, nystatin, and dexamethasone) was also used every four hours a day to control the pain of oral mucositis. Systemic painkillers were used to control severe pain of mucositis when indicated.

For those who developed diarrhea, exclusion of infectious etiology was done by testing Clostridium difficile toxin in stool, stool analysis, and culture. Anti-motility agents such as loperamide were allowed in non -infectious diarrhea also octreotide was used either in subcutaneous interrupted doses or as a continuous infusion in some patients with severe diarrhea. For patients who tested positive for any infectious cause, the treatment was received according to the cause. Electrolyte repletion was administered according to daily serum levels to maintain normal ranges of potassium, calcium, and magnesium. Abdominal imaging, ultrasound, or CT scans were performed when indicated.

Supportive irradiated blood products were administrated when needed, and granulocyte colony-stimulating growth factors (G-CSF) at 10 μg/kg once daily from day + 6, then decreased to 5 μg/kg when ANC reach 1000 for the majority of patients but in some patients, G-CSF was postponed after day + 6 when the neutropenic fever was delayed as per our BMT unit protocol.

GI toxicity assessment

GI events were recorded daily from the first day of conditioning till hospital discharge. Assessment of oral mucositis symptoms and signs with detailed data about pain degree, oral intake tolerability, and the average caloric intake which was assessed roughly by observing the rest of the patient's daily meals. Symptoms of nausea, vomiting episodes, and diarrhea were documented. In our study, diarrhea was defined when watery or loose bowel habits occurred. Patient weight at admission and daily follow-up were documented, and anti-emetics/anti-diarrheal drugs used, the need for opiates to control

mucositis pain, electrolyte imbalances, and the need for total parenteral nutrition were also recorded to assess the severity of GI toxicities. The grades of GI toxicities were done according to the Common Terminology Criteria for Adverse Events (CTCAE v4.0) [6]. The severity of upper GI symptoms (oral mucositis, nausea and vomiting) was assessed based on pain degree, oral intake, weight loss, and need for prolonged IV hydration or total parenteral nutrition. The severity of diarrhea was assessed according to the duration and number of episodes.

Study definitions

Severe GI toxicity was defined as grade 3 diarrhea and grade 2 or higher upper GI symptoms (oral mucositis, nausea, and vomiting).

OS was defined as time to death or last contact for survivors. TRM was defined as death during the first 100 days post-transplant. Neutrophil engraftment was defined as an absolute neutrophil count > 500/mL for 3 consecutive days, and platelet engraftment was defined as a platelet count > 20,000/mL for 3 consecutive days without any platelet transfusions [7].

Statistical analysis

The collected data were organized, tabulated, and statistically analyzed using SPSS software statistical computer package for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). For numerical values; the range, mean, median, and standard deviations were calculated. The differences between mean values were tested using the *t* test while the Mann–Whitney test (*U*) was used for other variables where data were not normally distributed. For categorical variables, the number and percentage were calculated and differences between subcategories were tested using the chi-square test. When chi-square was not appropriate, Fisher and Monte Carlo exact tests were used as appropriate. The level of significance was adopted at $p < 0.05$.

Results

A total of 47 adult patients with adequate data, received ASCT using melphalan-based conditioning at our center from January 2018 to December 2022. In all, three patients were excluded, two patients died before engraftment and one patient was diagnosed with a large hiatal hernia as a cause of vomiting.

Baseline characteristics of the study participants

The patient's baseline characteristics are described in Table 1. The age ranged from 20 to 69 years with a median age at transplant of 50 years. Twenty–four (51.1%) patients were males and 23(48.9%) were females.

Table 1 Baseline characteristics of the patients

Characteristic	Value (*n* = 47)
[a]Patient age (years)	50 (20–69)
Patient sex	
Males	24 (51.1)
Females	23(48.9)
Disease type	
Multiple myloma	23 (48.9)
Lymphoma:	24 (51.1)
Anaplastic T cell lymphoma	2 (4.3)
Breast lymphoma	1 (2.1)
DLBCL	10 (21.3)
Hodgkin lymphoma	9 (19.1)
Mantle lymphoma	2 (4.3)
Performance status	
0	40 (85.1)
1	7 (14.9)
Disease status at transplant	
CR	43 (91.5)
Refractory	4 (8.5)
Conditioning	
BEAM	22 (46.8)
LEAM	2 (4.3)
High-dose melphalan	23 (48.9)
Melphalan dosage	
200 mg/m^2	23 (48.9)
140 mg/m^2	24 (51.1)
Dose of CD34 cells (10^6/kg)	4.15 (2.3–10)
Pre-transplant comorbidities	
No	37 (78.7)
Yes	10 (21.3)
Weight at admission (kg)	80 (54–122)
[a]Diagnosis to transplant lag period (month)	13 (8–36)

[a] Values are expressed as median (range) and *n* (%)

Twenty-three (48.9%) patients were transplanted for myeloma with melphalan dose 200 mg/m^2 while 24(51.1%) patients received BEAM and LEAM with melphalan 140 mg/m^2 for lymphoma. All patients had adequate performance status and 91.5% of them were in complete remission at the time of transplant.

Ten patients were reported to have pre-transplant comorbidities which included diabetes, hypertension, and compensated chronic liver disease. The time from diagnosis to transplantation ranged from 8 to 36 months.

GI toxicities

Oral mucositis was nearly universal. Forty-four patients developed mucositis which ranged from grade 1 in 25(53.2%), grade 2 in 36.2%, and only 2 patients

developed grade 3 mucositis which requires adding opioid analgesia. Less mucositis was observed in patients who continue the cryotherapy for a longer duration after melphalan infusion. Thirty-seven patients received anti-emetic prophylaxis with ondansetron with or without dexamethasone, and an aprepitant was added for 10 patients only. Most of the patients experienced upper GI symptoms, grade 2 and grade 3 nausea occurred in 36.2% and 4.3% respectively. Thirty-eight (80.9%) of patients developed vomiting episodes with a median 2 days (range 1–4), grade 1 and grade 2 vomiting occurred in 40.4% and 36.2% of the patients, respectively with only two patients with grade 3 vomiting. Forty–four (93.6%) of patients experienced diarrhea with a median of 3 days (range 2–8), with a range of 3–15 bowel movements per day. The median onset of diarrhea was on day + 3 after the transplant, and the day of maximum episodes of diarrhea was day + 7 (range 3–13). Of all patients, 42.6% had grade 3 diarrhea, 20 (42.6%) had grade 2 diarrhea, and 8.5% has grade 1 diarrhea. Twenty-two (46.8%) of patients received Octreotide as subcutaneous interrupted doses or as infusion and Loperamide for diarrhea. Those who received Octreotide infusion rather than subcutaneous doses had shorter diarrhea duration. Only five patients out of 47 patients had an infectious cause of diarrhea (Enteropathogenic E. coli) and no patients had clostridium deficilli infection. CT scans of the abdomen and pelvis were done in 10 patients due to severe symptoms, 6 of them show colitis and 2 patients had radiological evidence of typhilits which required special consideration for feeding and antibiotic strategy (Table 2).

Table 2 Incidence of GI toxicities among patients

Variable	Value *n* = 47))
Oral mucositis	
Negative	3 (6.4)
Grade 1	25 (53.2)
Grade 2	17(36.2)
Grade 3	2 (4.3)
Nausea	
Negative	6 (12.8)
Grade 1	22 (46.8)
Grade 2	17 (36.2)
Grade 3	2 (4.3)
Vomiting	
Negative	9 (19.1)
Grade 1	19 (40.4)
Grade 2	17 (36.2)
Grade 3	2 (4.3)
Duration (days)	2 (1–4)
Anti-emetic prophylaxis:	
Ondansteron alone	10(21.3)
Ondansterone plus dexamethasone	27(57.4)
Aprepitant, ondansterone plus dexamethasone	10(21.3)
Diarrhea	
Negative	3 (6.4)
Grade 1	4 (8.5)
Grade 2	20 (42.6)
Grade 3	20 (42.6)
Duration (days)	3 (2–8)
The day of maximum diarrhea episodes post transplant	+ 7 (3–13)
Use of octerotide and anti-motility drugs(Lopperamide)	22 (46.8)

[a] Values are expressed as median (range), and *n* (%)

Transplant outcomes and severity of upper and lower GI toxicities

The median OS among our patients was 9 months and no TRM during the first 100 days related to infectious or GI complications. All patients achieved engraftment with a median time to neutrophil and platelets engraftment was 14 and 19 days, respectively. Only 8 patients had non-enteric infections, 2 of them developed fungal sinusitis, pneumonia occurred in 4 patients, and 2 patients suffered from catheter-related infections.

The clinical impact of grade 2 or higher upper GI symptoms (oral mucositis, nausea/vomiting) was compared to the impact of less than grade 2. The duration of neutropenia and length of hospital stay after transplant were significantly higher in patients who developed upper GI symptoms ≥ grade 2. Significant faster engraftment was observed in patients with upper GI symptoms < grade 2, a median time to neutrophil and platelet engraftment was 14 days (range 10–17) and 16 days (range 13–25) respectively, versus 19 and 22 days in those developed upper GI symptoms ≥ grade 2. Weight loss from admission and transfusion requirements were significantly lower in patients with upper GI symptoms < grade 2. The overall survival, duration on antibiotics, hypoalbuminemia, and incidence of renal impairment were similar in both groups (Table 3).

Similar clinical consequences were examined to compare the impact of grade 3 diarrhea over those with diarrhea ≤ grade 2. Duration of neutropenia, time to engraftment, length of hospital stay, hypoalbuminemia, renal impairment, weight loss, use of antibiotics beyond prophylaxis, the incidence of electrolyte imbalance, and transfusion requirements, all these variables were significantly higher in the group of grade 3 diarrhea. The use of anti-diarrheal agents was significantly higher in grade 3 diarrhea (85% versus 18.5%) in those who developed diarrhea grade ≤ 2. The severity of diarrhea had no impact on overall survival (Table 4).

Table 3 Relation between transplant outcomes and severity of upper GI symptoms

Outcome	Upper GI symptoms < grade 2 ($n=28$)	Upper GI symptoms ≥ grade 2 ($n=19$)	*p* value
Overall survival (month)	9(3–30)	9(3–32)	0.819
Neutropenic fever (days)	5(4–9)	8(4–13)	0.001
Neutrophil engraftment (days)	14(10–17)	19(11–30)	0.001
Platelet engraftment (days)	16(13–25)	22(17–36)	0.001
Days on antibiotics beyond prophylaxis	5(4–9)	6(4–10)	0.603
Duration of hospital stay (days)	19(17–25)	26(22–33)	0.041
RBCs transfusion (unit)	1(0–4)	3(1–4)	0.001
Platelet transfusion (unit)	12(6–36)	28(12–40)	0.001
Weight reduction from admission (kg)	3(0–5)	5(1–8)	0.001
Electrolyte imbalance			0.001
Negative	21(75)	0(0)	
Hypokalemia	6(21.4)	11(57.9)	
Hypokalemia plus hypomagnesemia	1(3.6)	8(42.1)	
Hypoalbuminemia			0.155
No	24(85.7)	13(68.4)	
Yes	4(14.3)	6(31.6)	
Renal impairment			0.163
No	25(89.3)	14(73.7)	
Yes	3(10.7)	5(26.3)	

Values are expressed as median (range) and *n* (%)

Table 4 Relation between transplant outcomes and severity of diarrhea according to grade

Outcome	Diarrhea ≤ grade 2 ($n=27$)	Diarrhea grade 3 ($n=20$)	*p* value
Overall survival (month)	8(3–30)	9(3–32)	0.730
Neutropenic fever (days)	5(4–13)	9(4–13)	0.003
Neutrophil engraftment (days)	14(10–20)	17(11–30)	0.002
Platelet engraftment (days)	16(13–25)	20(16–36)	0.001
Days on antibiotics beyond prophylaxis	7(4–10)	12(7–19)	0.003
Duration of hospital stay (days)	20(18–30)	28(18–40)	0.015
RBCs transfusion (unit)	1(0–4)	3(1–4)	0.001
Platelet transfusion (unit)	12(6–36)	27(12–40)	0.012
Weight reduction from admission (kg)	3(0–5)	5(1–8)	0.001
Electrolyte imbalance			0.001
Negative	20(74.1)	1(5)	
Hypokalemia	6(22.2)	11(55)	
Hypokalemia + hypomagnesemia	1(3.7)	8(40)	
Hypoalbuminemia			0.047
No	24(88.9)	13(65)	
Yes	3(11.1)	7(35)	
Renal impairment			0.041
No	25(92.6)	14(70)	
Yes	2(7.4)	6(30)	
Use of anti-motility drugs and octerotide			0.001
No	22(81.5)	3(15)	
Yes	5(18.5)	17(85)	

Values are expressed as median (range) and *n* (%)

Factors affecting the severity of GI toxicity

We examine the effect of patient factors, disease type, and melphalan dose on the severity of upper and lower GI toxicities among our patients. No statistically significant difference was found between patients aged more than 50 years and those below 50 years in the incidence of grade 3 diarrhea or upper GI symptoms ≥ grade 2. Females were affected more with both grade 3 diarrhea and upper GI symptoms ≥ grade 2 (65% and 37%) versus (63.2% and 39.3%), respectively but no significant difference could be detected. Grade 3 diarrhea was more common in lymphoma patients but without statistical significance (55% versus 45%, $p=0.508$). Melphalan dose of 200 or 140 mg/m^2 did not affect the severity of GI toxicities in a statistically significant manner (Table 5).

Discussion

ASCT is considered the standard of care therapy for patients with relapsed/refractory hematological malignancies. Pre-transplant conditioning with a melphalan-based regimen is widely used, with effective myeloablative properties [8]. However, individual sensitivity to melphalan varies, and many patients experience severe toxicities [9]. GI complications remain the most common extra-hematological side effects which can increase patients' morbidity after ASCT with a high incidence of infections, and electrolyte imbalances and impair their ability to consume adequate calories with the possibility of parenteral nutrition needs [10]. In the present study, we evaluate the GI toxicities developed in our patients after ASCT using conditioning with melphalan in 2 different doses and its effect on transplant outcomes.

GI toxicities were developed in the majority of our patients with different degrees of severity. Significantly delayed engraftment, a longer hospital stay, increased antibiotics and transfusion requirements as well as octreotide ± loperamide doses, and also prolonged febrile neutropenia were observed in patients who developed grade 3 diarrhea and ≥ grade 2 upper GI symptoms. Similar OS and TRM at 100 days were observed in all patients irrespective of the severity of GI toxicities. Melphalan dose, patient's age/sex, and disease type were not associated with a significant difference in the severity of upper and lower GI symptoms.

Vokurka and colleagues noticed similar results; oral mucositis was detected in 62% of patients who received ASCT with different melphalan doses with no significant difference observed between the median melphalan dose and the severity of mucositis [11].

In a recent study by Gordillo et al., who carried out a retrospective study on 100 consecutive ASCT recipients using melphalan, they noted similar results. GI complications affect the majority of patients, with 97% of the patients developing diarrhea, and 74% had ≥ grade 2 diarrhea. Grade 2 nausea and vomiting developed in 63% of their patients. They also reported a longer hospital stay, greater use of antibiotics, and electrolyte repletion in those with severe GI toxicity. Melphalan dose did not correlate with the severity of GI symptoms. However, they found that plasma cell neoplasm, female sex, older age, and poor renal function were independent risk factors for severe upper and lower GI toxicity, which was against our findings [12].

Unlike our results, authors of previous studies also noted an increased GI toxicity of melphalan in patients

Table 5 Association between patient factors, disease type, and melphalan dose with severity of GI symptoms

Variable	Upper GI symptoms < grade 2 (*n* = 28)	Upper GI symptoms ≥ grade 2 (*n* = 19)	*p* value	Diarrhea ≤ grade 2 (*n* = 27)	Diarrhea grade 3 (*n* = 20)	*p* value
Age			0.312			0.474
< 50	12(42.9)	11(57.9)		12(44.4)	11(55)	
≥ 50	16(57.1)	8(42.1)		15(55.6)	9(45)	
Sex			0.108			0.058
Male	17(60.7)	7(36.8)		17(63)	7(35)	
Female	11(39.3)	12(63.2)		10(37)	13(65)	
Disease			0.440			0.642
Lymphoma	13(46.4)	11(57.9)		13(48.1)	11(55)	
Multiple myeloma	15(53.6)	8(42.1)		14(51.9)	9(45)	
Melphalan dose			0.440			0.642
140 mg/m^2	13(46.4)	11(57.9)		13(48.1)	11(55)	
200 mg/m^2	15(53.6)	8(42.1)		14(51.9)	9(45)	

Values are expressed as median (range) and *n* (%)

with renal impairment and those aged older than 70 years [13]. Some authors reported increased GI toxicity in females, due to possible lower melphalan clearance in female patients compared to male patients [14]. Nath CE, et al., found higher incidence and severity of upper GI symptoms with higher melphalan doses [15].

These findings were against our results, which may be explained as the majority of our patients were less than 60 years with good renal functions; also, we did not measure the pharmacokinetics or dynamics of melphalan in our patients which may provide data about variable patient's response. High inter-patient variability in pharmacokinetics after melphalan administration has been observed and the risk factors of drug adverse events, which may be highly variable among patients, are not fully understood in clinical studies [16].

It should be noted that none of our patients were given keratinocyte growth factors or amifostine for mucositis prophylaxis, also we did not use a propylene glycol-free formulation of melphalan as these drugs were not available in our country at the time of the study. However, in recent research by Malek et al., the use of two amifostine doses of 740 mg/m^2 before ASCT was associated with a significant reduction in grade 2 and higher upper and lower GI toxicities without any effect on engraftment or anti-myeloma efficacy of melphalan [17]. Using propylene glycol-free glycol form has the advantages of improved solubility, stability, and bioavailability with less mucositis, febrile neutropenia, and transfusion requirements than usual melphalan formulation [18].

Conclusion

Melphalan-based regimens had a potent anti-tumor effect and provide sufficient immunosuppression facilitating engraftment, with different degrees of GI toxicity. Severe GI toxicity was associated with significant clinical consequences such as delayed engraftment, higher transfusion requirements, a longer hospital stay, more weight loss, and also prolonged febrile neutropenia. Females and lymphoma patients had more severe GI toxicities without statistically significant differences. In our study, melphalan dose, patient's age/sex, and disease type were not identified as significant risk factors for the severity of upper or lower GI toxicities.

Study limitations

We must address the limitations of this work. This is a retrospective study with a small number of patients, we did not use higher doses of melphalan above 200 mg/m^2 and this may limit the ability to identify certain risk factors of melphalan GI toxicity. The cytoprotective agent amifostine was not used in this study, which may affect the incidence and severity of upper GI symptoms. Despite these limitations, it is the first study to be conducted from our BMT center in Delta, Egypt about GI toxicity in ASCT recipients. Our data might provide the basis for further larger prospective studies aiming at improving GI prophylaxis/treatment in ASCT patients to decrease the toxic effect and keep the beneficial antitumor effect of melphalan which may improve transplant outcomes, and patient's quality of life and decrease transplant costs.

Abbreviations

ASCT	Autologous stem cell transplantation
GI	Gastrointestinal
OS	Overall survival
TRM	Transplant-related mortality

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Authors' contributions

MMA, FA, and RGM contributed to the concept and data collection. MMA wrote the manuscript. MMA and RGM shared in the revision of the article. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The baseline data that support the finding of this work were obtained from the BMT unit registry of Tanta Educational Hospital after permission.

Declarations

Ethics approval and consent to participate

The study was conducted by the stipulations of the local ethical and scientific committee of Tanta University, Egypt. Ethics approval code number: 35591. The files were retrieved after concealing the personal details of patients to keep the confidentiality of data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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