Case 1:

A Case Report on Diclofenac Induced Stevens Johnson Syndrome

Sateesh Kumar Reddy K*, Shanmuga Kumar SD, Vijay Raghavendra NC and Sudheer Kumar K

Abstract

Stevens Johnson syndrome is a serious systemic disorder with the potential for severe morbidity and mortality. Stevens Johnson syndrome is a rare vesiculobullouus disease characterized by acute cutaneous eruptions that involves the skin and mucous membrane. It is a type 4 hypersensitivity reaction with severe skin symptoms and also often accompanied by complications in numerous organs such as liver, kidney and lungs. By considering the extend of skin detachment the Stevens Johnson syndrome and Toxic epidermal necrosis are classified that is with the degree of epidermal detachment less than 10% of body surface being classified as Stevens Johnson syndrome, greater than 30 as Toxic epidermal necrosis and 10-30% as Stevens Johnson syndrome/Toxic epidermal necrosis overlap. The most common cause of SJS were drugs they account for about 80% of the cases among them allopurinol, carbamazepine, Phenobarbital, phenytoin, Valproic acid lamotrigine, antibiotics oxicam (NSAIDS) and rarely by microorganisms like mycoplasma pneumonia and herpes simplex virus, here we report an adverse drug reaction with diclofenac in a 12 years old patient.

Keywords

Stevens johnson syndrome, toxic epidermal necrosis, epidermal detachment, diclofenac

Introduction

Adverse drug reactions has been accounts 6% of the total hospital admissions, this results in increase economic burden on health care system which is turn results in withdrawal of drugs from market.[1] These adverse drug reactions may vary from mild rashes to severe reactions such as Stevens Johnson's syndrome. Stevens Johnson's syndrome is a rare vesiculo bullous disease characterized by an acute cutaneous eruption that involves the skin and mucosal membranes. It is a hypersensitive reaction characterized by skin rashes with hyper pigmentation and cutaneous target lesions involving blistering, erosions over face, trunk, and limbs. Some studies incidence of SJS ranges from 1.2-6 patients per million per year. Studies shows that women were more likely to have TEN and men with SJS.[2] Considering the extent of skin detachment the SJS and TEN are classified as following, the degree of epidermal detachment less than 10% of body surface area being classified as SJS, greater than 30% as TEN and 10-30% as SJS/TEN overlap.[3] SJS is a serious systemic disorder with the potential for severe morbidity and mortality. SJS has the mortality rate of approximately 1-5%. However, when more than 30% of body surface area sloughing is present, the mortality rate is between 25% and 35%.[4] These in addition to severe skin symptoms, often accompanied by complications in

numerous organs, such as liver, kidney, and lungs. Patient may initially present with SJS, which subsequently evolves into TEN or SJS-TEN overlap. Diagnosis of disease is mainly by clinical signs and histopathology of the lesions. The most common etiologic factors of SJS were drugs. They account for about 80% of cases. Among the drugs were carbamazepine, Phenobarbital, phenytoin, Valproic acid, allopurinol, lamotrigine, oxicam, sulfonamide antibiotics are most commonly implicated.[5] Other than drugs infections such as mycoplasma pneumonic and herpes simplex virus are commonly reported.[6] The pathobiology of SJS involves a specific immune reaction where human leukocyte antigen (HLA) alleles specific for certain drugs in defined populations are involved in the activation of cytotoxic T-lymphocytes and natural killer cells. Upon the activation, various cytotoxic and immunological signals, including but not limited to Fas/Fas ligand, perforin/ granzyme B and granulysin are launched to mediate the dissemited keratinocyte death and detachment of epidermis in SJS/TEN. If this separation was not treated then it can lead to large denuded areas that cause extreme pain, massive loss of fluid, protein, bleeding, evaporative heat loss with subsequent hypothermic and infection.[7] The characteristic pattern presents with necrotic keratinocytes in either wide dissemination or full thickness necrosis of the epidermis. Vacuolization bleeding to sub epidermal blistering is found in the basal membrane. A superficial, often perivascular, lympho histocytic infiltrate can be seen in the upper dermis. While various amount of eosinophil were observed in the infiltrate of tissue biopsies of the patients with Erythema multiforme major, Stevens Johnson syndrome and Toxic epidermal necrosis. Other investigations reported less epidermal necrosis, more dermal inflammation and more exocytosis in erythema multiform major compared with Stevens Johnson syndrome.[8] The success of the treatment depends on the early recognition of the condition, prompt removal of the causative medications and intensive supportive care in a well-equipped hospital. Several agents with antiinflammatory or immunosuppressive properties have been tried to alter the course of the disease but no single agent has their efficacy clearly proven by clinical trials.[9] Diclofenac is most widely used NSAID for its analgesic activity. A literature search revealed that meager cases of mucocutaneous drug reaction secondary to NASID therapy were reported.[10] In this investigation, we study a case of Diclofenac induced Stevens Johnson syndrome. A 12 year old child was admitted into the pediatric department of SVS medical college and hospital and presented with the symptoms of ulceration of mouth, lips and oral mucosal ulceration, sore throat and also fever since 4 days. In addition to this the child had reddish purple maculopapular lesions on the stomach and forearms and his eyes were congested. Patient's degree of epidermal detachment has found to be less than 10% of body surface area. In the patient medical history we found that patient has pain in the thigh region for which he has been treated with Diclofenac sodium-50 mg Bid. All the clinical examination including neurological examination and bactericidal culture has been done. The results of skin biopsy showed derma epidermal separation and lymphocytic infiltration. Physical examination shows erosion over lips, dorsum of tongue with no genital involvement and increase in body temperature has been observed. Laboratory tests show complete blood picture Hemoglobin normal, elevated levels of WBC 16500 cells/cumm. Increase C. reactive protein to about 12 mg/dl. T zank test was done and no herpes simplex virus found. Skin biopsy shows dermal epidermal separation. Based on the data obtained team of specialist including dermatologist confirmed that the diagnosis of SJS induced by Diclofenac. Immediately Diclofenac treatment was discontinued and was initiated treatment with the following medication.

Internal medication	External medication
1) Inj. hydrocortisone 190 mg IV BD for 1-3 days.	1) Siverex ointment, silver nitrate, antimicrobial 0.2%w/w topical BD for 3-5 days.
2) Tab. paracetamol 250 mg PO QID 3-5 days.	2) Candid mouth paint, clotrimazoleanti fungal 1% w/w topical BD 2-5 days.
3) Tab. fluconazole 150 mg PO OD 2-4 days.	3) Liq paraffin- emollient, TID.
4) Inj. Avil-pheniramine malate, 2 cc IV BD 1-5 days.	4) Topical lidocaine 2%.
5) Ciprofloxacin eye drops.	
6) Syp. Azithromycin-200 mg/5 ml PO OD 3-5 days.	

Lesions were monitored during treatment and after 5 days of treatment there was no evidence of cutaneous or mucosal ulcers. Discharge medications include pheneramine malate, paracetamol, sliver nitrate, liquid paraffin.

Discussion

Physicians must warn their patients about the possible side effects. SJS/TEN is a rare and unpredictable reaction to medication. SJS associated with NSAID is rare. Steren reported case series of 135 cutaneous reactions secondary to use of NSAIDS in USA.[11] A study with adverse reactions of SJS due to NSAID's show that the NSAID, oxicam derivatives appeared to have the greatest association with SJS and TEN in USA and with other NSAID's reported were much lower. The exact pathogenesis of SJS and TEN remains to be elucidated but apoptotic mechanisms, including involvement of cytotoxic T-cell tumor necrosis factor-α, and Fas (CD 95), Fas ligand interactions are considered to be relevant to these disease.[12] The common complications in SJS/ TEN patients are septicemia, secondary infections, pneumonia and acute renal failure. Antimicrobials, anti convulsants, and antipyretics were commonly reported offending group of drugs for SJS/TEN. Ethnic pharmacogenetic difference plays a major role in drug reaction towards patients. The use of screening prior to initiation is a promising step to further reduce the mortality and morbidity of such reactions. Stevens Johnson syndrome is a very rare complication of Diclofenac use but due to its dangerous consequences, practitioners should be aware of it and give information to their patients.

Case 2:

A case report of rhino-facial mucormycosis in a non-diabetic patient with COVID-19: a systematic review of literature and current update

Abstract

Background

COVID-19 disease may be associated with a wide range of bacterial and fungal infections. We report a patient with COVID-19 infection who developed rhino-facial mucormycosis during treatment with corticosteroids.

Case presentation

A 59-year-old non-diabetic male patient was admitted with a diagnosis of COVID-19 based on positive RT-PCR and CT of the lungs. Due to sever lung involvement, he was treated with methylprednisolone. The patient was re-admitted to hospital, due to nasal obstruction and left side facial and orbital swelling, several days after discharge. In sinus endoscopic surgery,

debridement was performed and the specimens were sent to pathology and mycology laboratories. A nasal biopsy showed wide hyphae without septa. The sequenced PCR product revealed *Rhizopus oryzae*. Despite all medical and surgical treatment, the patient died. In addition, the characteristics of patients with COVID-19-associated mucormycosis were reviewed in 44 available literatures. In most studies, diabetes mellitus was the most common predisposing factor for mucormycosis.

Conclusion

Our report highlights the need for assessing the presence of mucormycosis in patients with COVID-19 and also it shows that physicians should consider the potential for secondary invasive fungal infections in COVID-19 cases.

Peer Review reports

Background

COVID-19 is a viral disease of the respiratory tract that continues to be a major health issue worldwide. The disease is associated with common symptoms such as fever, dry cough, fatigue, and shortness of breath and sometimes in severe cases, leads to acute respiratory distress syndrome (ARDS) [1]. On the other hand, the use of corticosteroids to modulating lung injury and reduce mortality in COVID-19 patients may be exposes the patient to opportunistic bacterial and fungal infections [2].

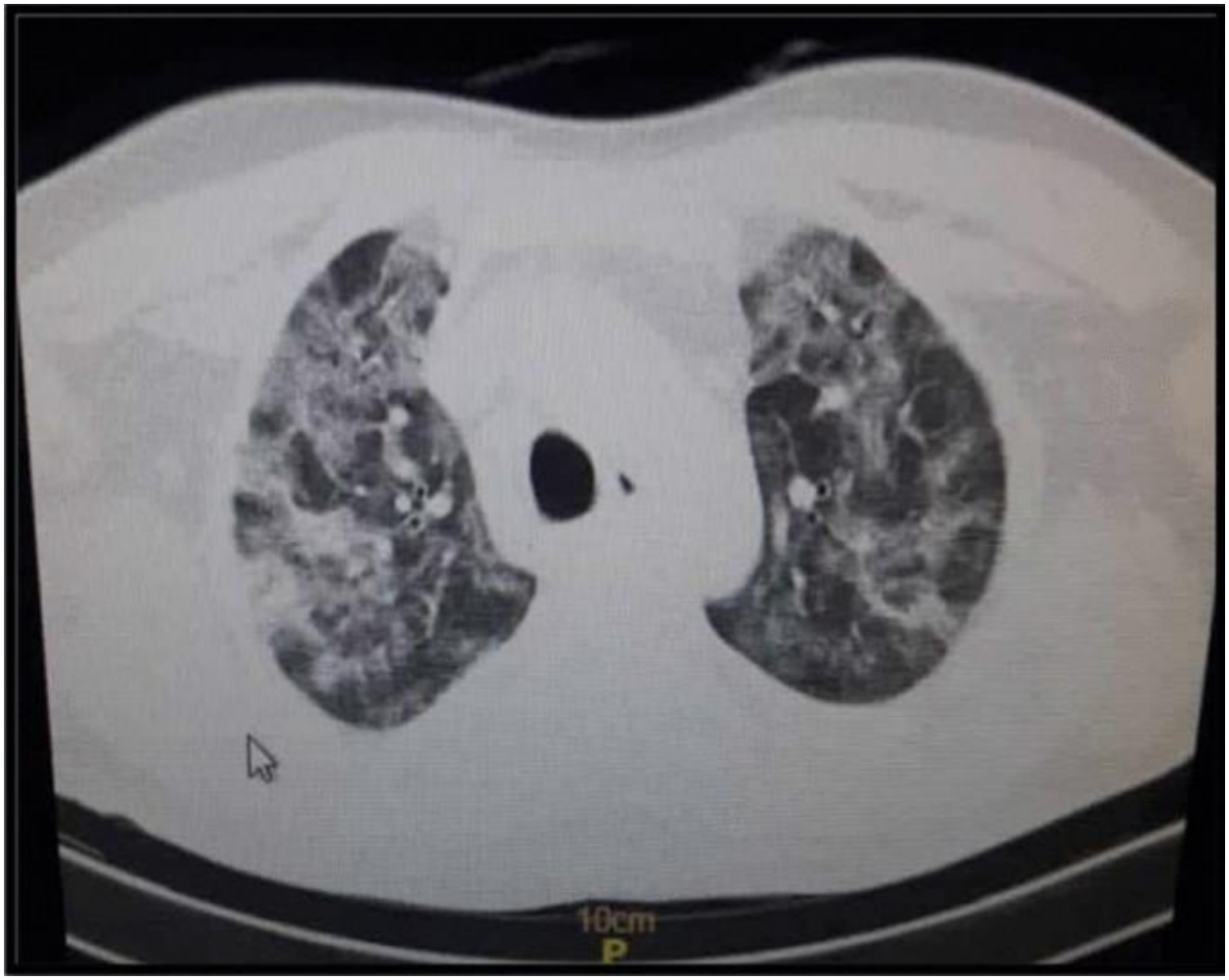
Invasive pulmonary aspergillosis is one of the fungal diseases that complicates COVID-19 manifestations [3]. Moreover, mucormycosis as an opportunistic fungal infection can progress rapidly in immunocompromised patients. The most common clinical form of this fungal infection is rhino-cerebral mucormycosis [4]. We reported a case of rhino facial mucormycosis in a

59-year-old non-diabetic male patient with COVID-19 following corticosteroid treatment, which eventually resulted in death.

Case presentation

A 59-year-old non-diabetic male patient without any underlying disease with clinical symptoms of cough, shortness of breath, and oxygen saturation of 76% was admitted to Razi Hospital, Qazvin, Iran. His vital signs included body temperature of 37.6 °C, blood pressure value of 140/85 (mm Hg) and oxygen saturation of 76%. Positive results of chest X-ray test (CXR), computed tomography (CT) scan of lungs and positive reverse transcriptase polymerase chain reaction (RT-PCR) showed a definite diagnosis of COVID-19 (Fig. 1).

Fig. 1



Computed tomography (CT) scan of the chest of a patient with COVID-19 shows multiple patchy ground-glass opacities

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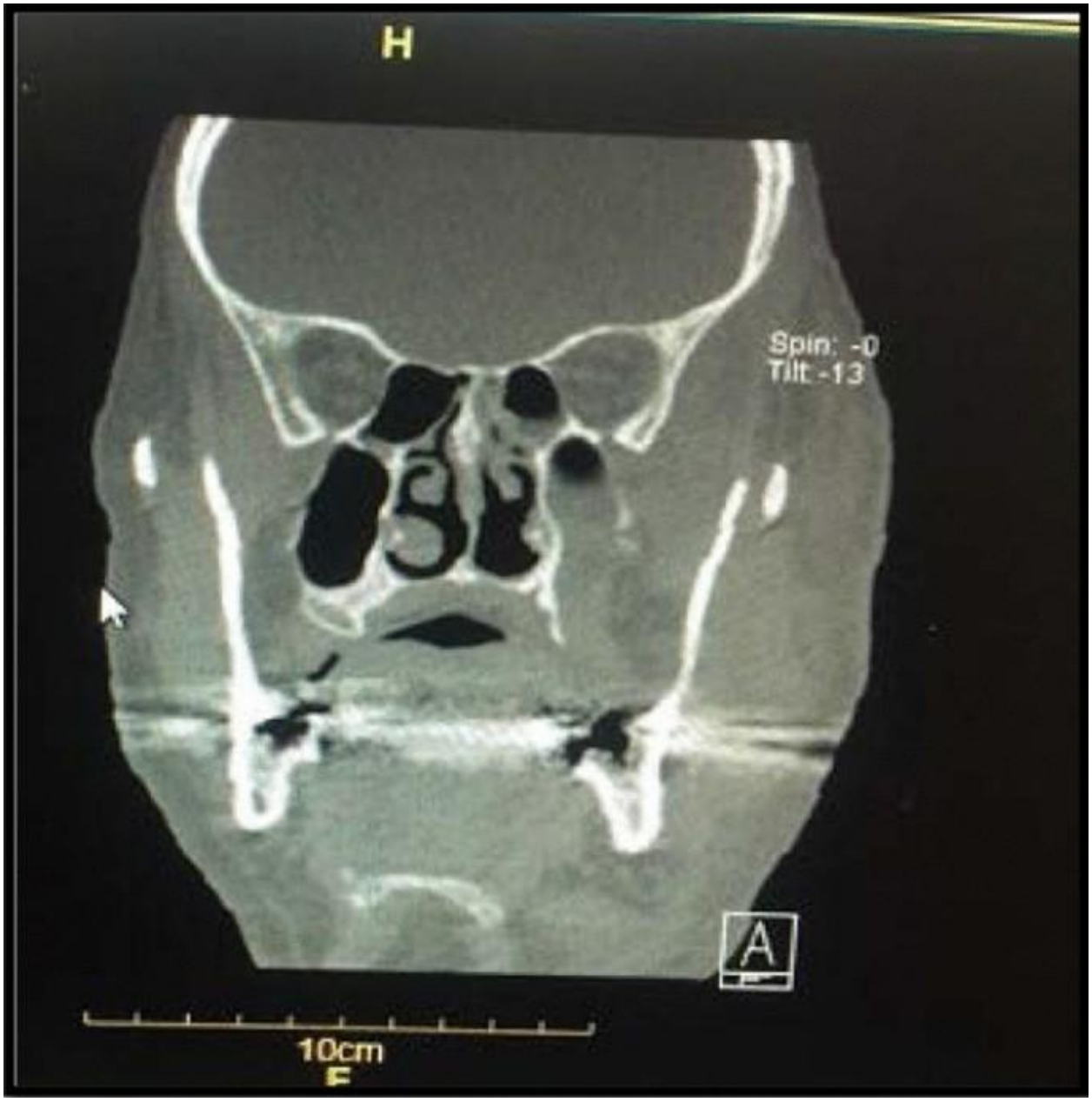
He was treated with remdesivir injection at a dose of 250 mg stat and then 100 mg daily. The patient was under supportive care for six days, and thereafter methylprednisolone was administered at a dose of 250 mg stat and then 125 mg for 3 days. After 10 days, the patient was discharged while he was relatively in good general condition. Four days after his discharge, the patient was re-admitted to hospital because of nasal obstruction and left side facial and orbital swelling. Table 1 shows the laboratory findings of the patient during both COVID-19 and mucormycosis. Subsequently, the patient visited by an infectious disease specialist and due to the involvement of the left ethmoid, sphenoid, and maxillary sinuses, a CT scan was performed (Fig. 2). In sinus endoscopic surgery, by Rhinologist, severe involvement and necrosis of the left side lateral nasal wall, floor, and septum as well as left ethmoid and sphenoid sinuses were observed and also destruction of the left orbital floor and medial wall were observed. Since clinical results confirmed the possibility of mucormycosis in the patient, treatment with IV liposomal amphotericin B (3 mg/kg/day, according to local guidelines [5]) was started. In addition, the patient underwent daily paranasal sinuses debridement and irrigation with diluted amphotericin B. Biopsy of sinonasal area was made and the specimens were sent to both pathology and mycology laboratories. Examination of the results with haematoxylin and eosin (H&E) staining and direct experiment with 10% potassium hydroxide (KOH) showed irregular hyphae, wide and aseptate (Fig. 3).

Table 1 The measured hematological biomarkers in blood of the patient

Fig. 2



CT scan shows involvement of the left ethmoid, sphenoid, maxillary and paranasal sinuses in a patient with mucormycosis

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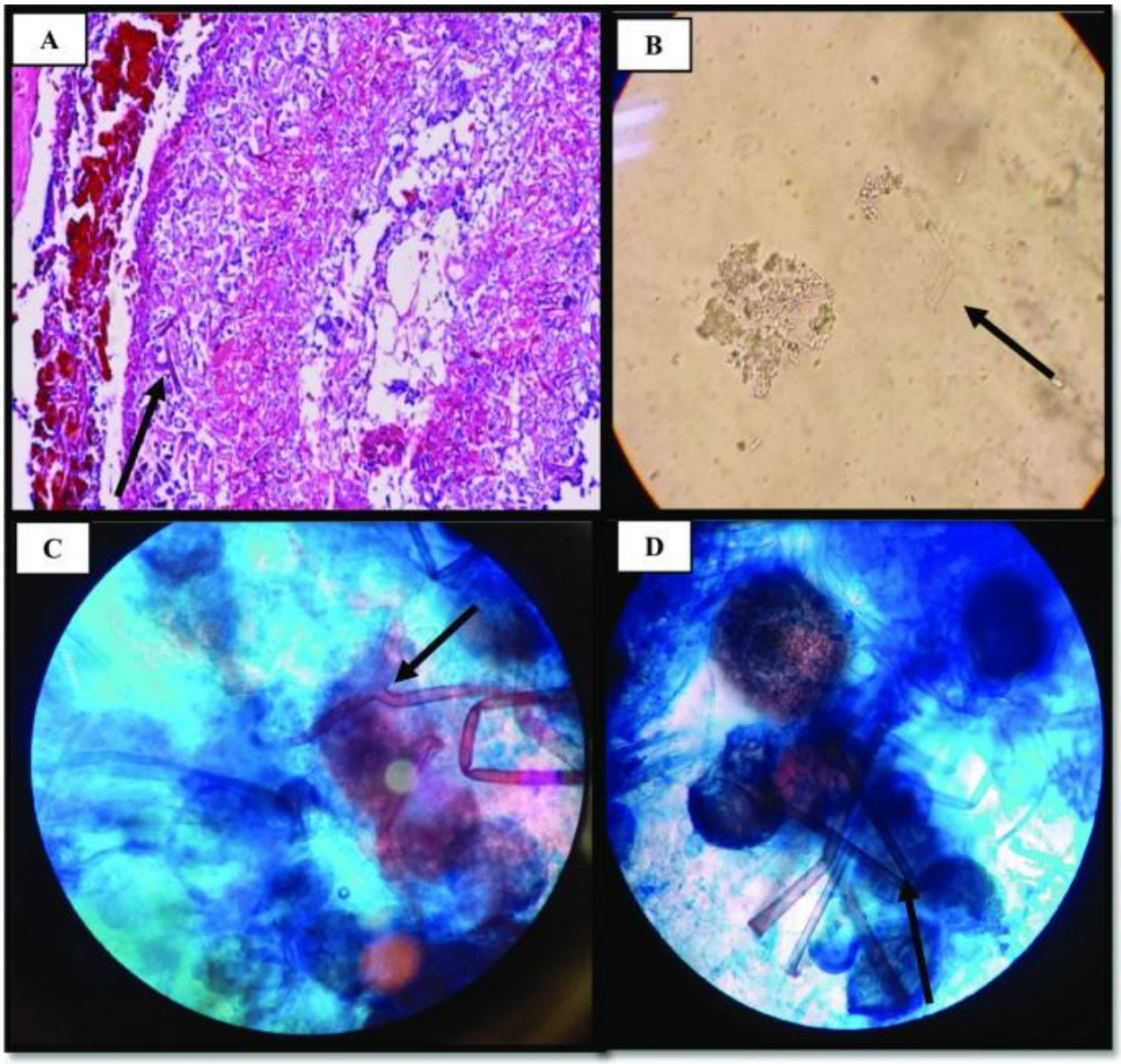
Fig. 3



a Presence of irregular and non-septate hyphae in H&E staining of pathology. b Observation of broad aseptate hyphae in surgical debridement in direct examination (10% KOH). c and d Lactophenol cotton blue (LCB) mount showed nonseptate hyphae, rhizoids and spore-filled sporangiophores

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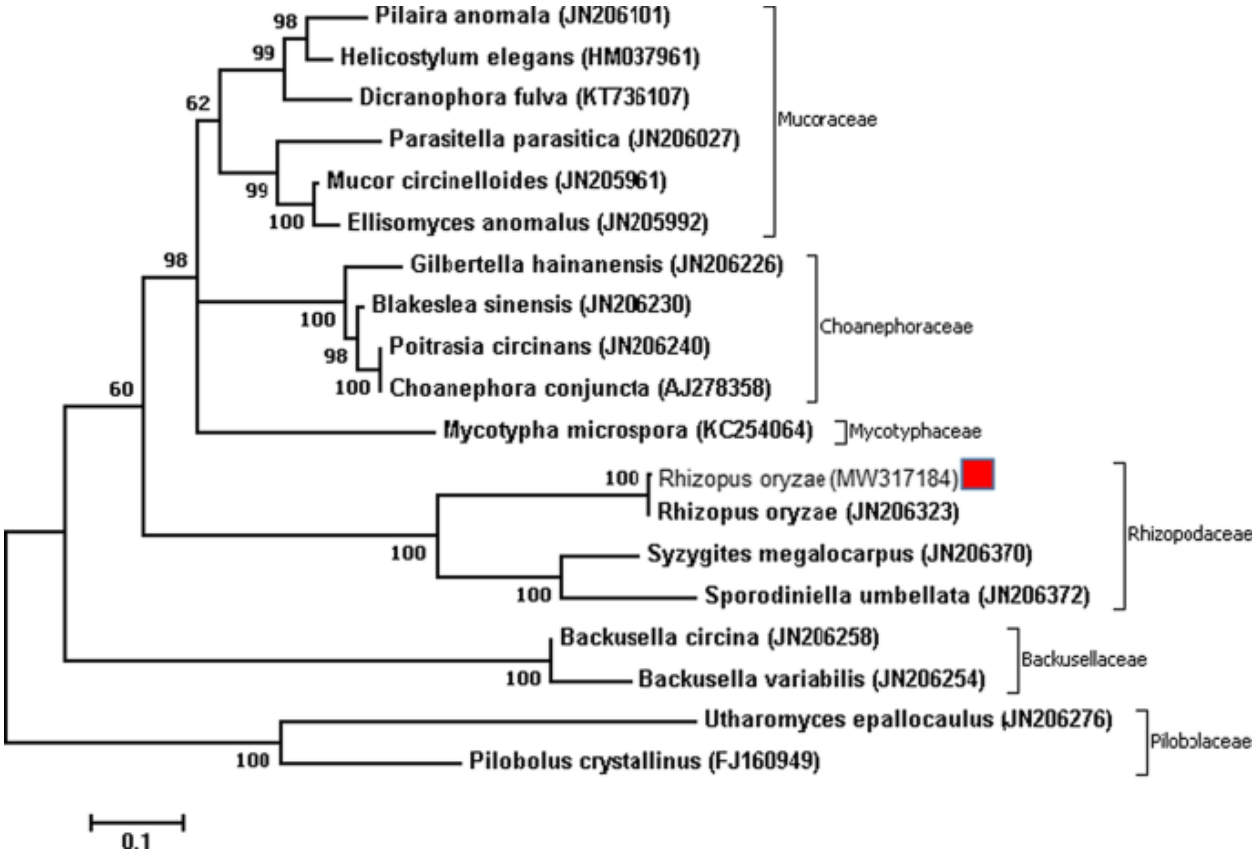
In addition, the sample was inoculated on PDA (Sigma-Aldrich,UK) and was incubated for 4–5 days at 37 °C. After colony growth, non- septate hyphae, rhizoids and spore-filled sporangiophores were observed in slides prepared with LCB (Fig. 3). The antifungal susceptibility testing was performed in 96-well plates by following the M38-A2 guidelines of the CLSI for in vitro testing. MIC values against AMB, ITC and VRC were 0.5 mg/mL, 16 mg/mL and 32 mg/mL, respectively. In the next step, DNA extraction was carried out using the glass beads and phenol:chloroform:isoamyl alcohol (25:24:1) method, previously described [6]. The fungal isolate was identified by molecular analysis of ITS1-5.8S-ITS2 region using the primers for ITS1 (5′-TCCGTAGGTGAACCTGCGG-3′) and ITS4 (5′-TCCTCCGCTTATTGATATGC-3′). The sequenced PCR product showed 100% sequence identity with *R. oryzae* and it was registered in the GenBank database under the assigned accession number MW317184. Sequence was aligned with using the ClustalW algorithm as implemented in Bioedit version 7 (http://www.mbio.ncsu.edu/BioEdit/bioedit.html). The molecular diversity of the sample was estimated by phylogenetic analysis via MEGA7 software. In order to compare the sequences with available DNA sequences in GenBank, the nucleotide BLAST with the BLASTn algorithm was applied through CLUSTAL omega (https://www.ebi.ac.uk/Tools/msa/clustalo/). The protocols were conducted based on the ML method using the Tamura-Nei model. The number of bootstrap replications was considered to be 1000 (Fig. 4). Because of the progression of the disease and the involvement of the cheeks and orbit, necrotic tissues were removed. Despite all measures, the patient unfortunately

expired on the seventh day of his admission due to loss of consciousness and involvement of central nervous system.

Fig. 4



The phylogenetic tree of isolates of *Rhizopus oryzae*. Based on ITS sequence from a patient with mucormycosis and GenBank sequences of some related species were estimated in MEGA7 using the ML analyses based on 1,000 bootstrap replications

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Discussion and conclusions

COVID-19 disease has a rapid and widespread distribution with mild to severe symptoms. Supportive care, corticosteroids and remedial drugs are good treatment options in COVID-19. On the other hand, due to the use of steroids, these patients may be susceptible to invasive mould infections. Furthermore, diabetes mellitus complicates the management of Covid-19 infection.

Mucormycosis is an acute fungal infection caused by the members of mucoraceae family. Mucormycosis in uncontrolled diabetic patients and immunocompromised is an opportunistic and fatal fungal disease [7]. The most common clinical manifestation of mucormycosis in immunocompromised patients is the rhino-orbito-cerebral form [8]. Infection begins in the nasal cavities and paranasal sinuses. The symptoms of mucormycosis include one-sided facial swelling, headache, fever, inflammation, eyelid drooping and black lesions on nasal that the disease spreads rapidly [9]. Infarction and necrosis of host tissues occur due to invasion of non-septate hyphae [10]. Methods for diagnosing mycromycosis include histopathology, direct testing, and culture of clinical specimens [11]. The first line of management of mucormycosis is recommended injection of liposomal amphotericin B. In case of intolerance of the treatment regimen or general weakness of the patient, azole compounds such as Posaconazole and Isavuconazole can be used [5].

The database search using the terms “COVID” OR “SARS-CoV2” OR “Coronavirus” AND "Mucor" OR “Zygomycosis” revealed a total of 44 articles. The characteristics of patients with COVID-19-associated mucormycosis were shown in Table 2.

Table 2 Characteristics of patients with mucormycosis and COVID-19 reported in the literature

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Review of literature published till June 2021 shows that the most cases are related to mucormycosis in COVID-19 patients was in India with 110 cases [12,13,14,15,16,17,18,19,20,21,22,23,24,25], followed by Iran (20 cases) [26,27,28,29,30], Turkey (12 cases) [31, 32], Egypt (11 cases) [33, 34], the United States and (10 cases) [35,36,37,38,39,40,41,42,43], the Netherlands (4 cases) [44], UK and Spain (2 cases) [45,46,47]. Furthermore, a case of mucormycosis in COVID-19 patients has been published from Brazil [48], Australia [49], France [50], Mexico [51], Italy [52] and Iraq [53]. Studies show that the median age of the patients was 53.4 years (range 22–86) with a higher prevalence of mucormycosis in men (75.7%). The association of mucormycosis with uncontrollable diabetes has been proven [54]. Diabetes mellitus was the most common predisposing factor (73.4%) for mucormycosis in COVID-19 patients [14, 15, 27, 32, 35, 44]. In 5 cases (2.8%), no risk factors for mucormycosis were reported [14, 21, 29, 37]. In our reported case, corticosteroid-related hyperglycemia was observed in a patient with no history of diabetes. Predisposing factors for mucormycosis include diabetes mellitus, neutropenia, corticosteroid use, and immunodeficiency, among which diabetes is the most common risk factor linked with mucormycosis [55]. The severity of COVID-19 infection and its dangerous consequences are higher in individuals with diabetes. Glucocorticoids reduce mortality in patients with COVID-19 by reducing cytokine storm. Nevertheless, corticosteroids can increase the risk of fungal and bacterial secondary infections [56]. Therefore, use of steroids should be avoided in mild to moderate COVID-19 cases as they lead to dangerous results. Reports indicate that 82% of patients received corticosteroids.

The mean duration from between diagnosis of COVID-19 and the onset of symptoms of mucormycosis was 15 days [15, 18]. Studies show that the most common clinical manifestation of mucormycosis is rhino-facial, followed by pulmonary and disseminated form. Herein, we report a case of mucormycosis in a 59-year-old male non-diabetic with COVID-19. The patient developed rhino-facial mucormycosis after the initiation of corticosteroid. The mean duration between diagnosis of COVID-19 infection and the onset of symptoms of mucormycosis was 15 days [13, 15, 57]. The present case indicates that in the presence of COVID-19, even short-term treatment with corticosteroids may be a predisposing factor in leading the patient to rhino-orbital mucormycosis. Studies show that glucose control, timely treatment with liposomal amphotericin B, and surgical debridement are effective in the management of mucormycosis. The prognosis of the disease depends on factors such as early diagnosis and management to limit the spread of infection into the intracranial space [5, 58]. This study, in line with the results of other studies, reveals that the possible occurrence of secondary invasive fungal infections in patients with COVID-19 infection should not be neglected. Effort to maintain blood sugar and the rational use of corticosteroids in COVID-19 patients is recommended to reduce the risk of mucormycosis.

Availability of data and materials

All data analyzed during this study are included in this published article.

Abbreviations

COVID-19:

Coronavirus disease 2019

ARDS:

Acute respiratory distress syndrome

H&E:

Hematoxylin and eosin

PDA:

Potato dextrose agar

CLSI:

Clinical and Laboratory Standards Institute

MIC:

Minimum inhibitory concentration

***R. oryzae* :**

Rhizopus oryzae

ML:

Maximum-likelihood

Case 3:

Bowel, lung, and retinal ischemia: Rare manifestations of leukostasis syndrome in a man with chronic lymphocytic leukemia—A case report and review of the literature☆

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Bowen He [a], Junid A. Naveed Ahmad [a], Connie J. Chen [b], David M. Aboulafia [c d]

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Abstract

Leukapheresis is a resource-intensive and high-risk treatment with unclear benefits when used for leukostasis syndrome in hematologic malignancies. In this case report and literature review we discuss the pathophysiology of leukostasis syndrome associated with chronic lymphocytic leukemia (CLL) and the rapidly evolving paradigm of CLL treatment through the lens of a

51-year-old man who was diagnosed with CLL. He presented with clinical manifestations of leukostasis syndrome with an absolute lymphocyte count of 522.6×109/L. We identified 15 additional cases of CLL-associated leukostasis syndrome in our literature review. Pulmonary and neurologic manifestations of leukostasis were most common. In combination with pharmacologic cytoreduction, leukapheresis was used successfully in most cases with few reports of complications. In the context of greater adoption of first line therapies for CLL that are known to induce transient leukocytosis, we explore leukapheresis as an adjunctive therapy that can rapidly reduce the lymphocyte count and in select instances possibly mitigate the effects of Bruton's tyrosine kinase inhibitor-induced hyperleukocytosis.

Previous article in issue

Next article in issue

Keywords

AcalabrutinibBTK inhibitorHyperleukocytosisLeukapheresisCase report

1. Introduction

Chronic lymphocytic leukemia (CLL) is a neoplasm of mature B lymphocytes with substantial variability in disease severity. Early-stage disease is often indolent and can be successfully monitored because immediate treatment does not significantly improve survival rates, which can be similar to that of the general age-matched population (CLL Trialists' Collaborative Group 1999). Clinical assessment and laboratory tests are employed as diagnostic and prognostic indicators of disease progression and help determine when treatment is necessary (Hallek et al., 2008). Symptomatic hyperleukocytosis (leukostasis) in patients with hematologic malignancy is generally considered an oncologic emergency with an early death rate as high as 40% if left untreated (Giammarco et al., 2017). Although leukostasis is extremely rare in

CLL, it too has been reported to cause severe morbidity and mortality (Oscier et al., 2012). Herein, we describe the case of a man with CLL who presented with retinal, gastrointestinal, and pulmonary leukostasis. His white blood count (WBC) at presentation was greater than 500 × 10_9/L and consisted almost exclusively of a population of mature and clonal B lymphocytes. We describe his clinical course and review the literature of this rare complication of CLL. We also discuss the pathophysiology and management of CLL-associated leukostasis syndrome. Although leukapheresis has been used to rapidly reduce the WBC in leukostasis, there is no conclusive evidence that this treatment increases life expectancy (Ganzel et al., 2012).

2. Case report

A 51-year-old man with hypertension and no recent laboratory assessments presented to a local emergency department (ED) in June 2019 for several days of left thigh cramping. A computerized tomogram (CT) revealed a 5.0 × 3.6 × 9.7 cm hematoma involving the antero-medial left thigh with active extravasation of contrast near the sartorius muscle. Subsequent magnetic resonance imaging (MRI) of the thigh showed no visible vascular malformations. His complete blood count (CBC) was notable for a WBC of 47.3 × 10_9/L (normal, 3.5-11.0 × 10_9/L) with 71% lymphocytes and 25% segmented neutrophils, hematocrit (HCT) 41% (normal, 39-50%) and platelet count of 131 × 10_9/L (normal, 150-400 × 10_9/L). Chemistry, liver tests and coagulation studies including prothrombin time (PT), partial thromboplastin time (PTT), thrombin time, fibrinogen level, and Von Willebrand disease screening were not suggestive of coagulopathy. Fluorescence-activated cell sorting (FACS) of peripheral blood lymphocytes confirmed this patient's leukocytosis was due to newly diagnosed CLL.

With conservative care, the patient's hematoma gradually resolved. His CBC remained stable during several follow-up visits, and his review of symptoms remained unremarkable. He was advised to follow up with his hematologist in three months. However, the patient lost medical insurance coverage and 14 months passed before he was seen again. At that visit, routine laboratory studies were notable for an increase in WBC to 159 × 10_9/L with declines in his HCT to 38% and his platelet count to 84 × 10_9/L. The patient was instructed to

return to his hematologist to reassess laboratory studies in three months' time but did not seek medical care until February 2021 when he presented to an ophthalmology clinic with seven days of progressive unilateral blurred left eye vision. His visual acuity was 20/25 in the right eye and 20/300 in the left eye. Fundoscopic exam was notable for scattered white-centered intraretinal hemorrhages in both eyes and a prominent intraretinal hemorrhage involving the fovea in the left eye, accounting for the patient's decreased visual acuity (Fig. 1A).

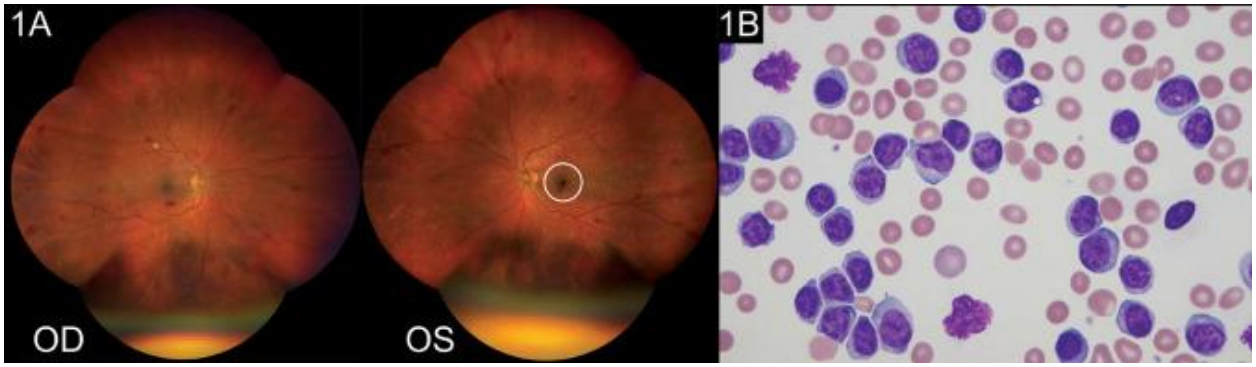

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Fig. 1

He urgently established care in our hematology clinic where his exam was notable for generalized pallor, scattered ecchymosis, and an enlarged spleen that was palpable several finger breadths below the left costal margin. His WBC had increased to 522.6 × 10_9/L with 97% lymphocytes (Fig. 1B). His HCT was 22%, platelet count was 84 × 10_9/L, hepatic transaminases were within normal limits, lactate dehydrogenase (LDH) was 354 U/L (normal, 125-243 U/L), and uric acid level was 5.7 mg/dL (normal, 3.5-8.0 mg/dL). The patient was instructed to go to the ED for anticipated admission to the hospital.

In the ED, he was afebrile, normotensive, and had a respiratory rate of 18 breaths per minute. Despite a subjective sense of shortness of breath, his oxygen saturation was 100% on room air. A CT of the chest, abdomen, and pelvis with intravenous contrast was obtained to further evaluate the patient's

dyspnea and acute lower abdominal discomfort. This revealed modest axillary adenopathy, an enlarged liver measuring 21 cm, and an enlarged spleen measuring 25 cm (Fig. 2A). Axial images of the chest were notable for subtle pulmonary interstitial infiltrates (Fig. 2B) and abdominal and pelvic cuts further demonstrated retroperitoneal and pelvic lymphadenopathy (Fig. 2C). Additionally noted was a segment of ischemic small bowel that was mildly dilated and demonstrated moderate wall thickening (Fig. 2D). A sputum analysis for bacterial pathogens and polymerase chain reaction (PCR) tests for viral pathogens including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) returned negative. A PTT was normal, and PT was 15.6 seconds (normal, 11.8-14.3 seconds) with an international normalized ratio (INR) of 1.2 (normal, 0.9-1.1). Laboratory studies were consistent with a hypoproliferative anemia and demonstrated normal ferritin, vitamin B12 and folate levels. There was no evidence of hemolysis. FACS of peripheral blood revealed a kappa-restricted B cell population that expressed CD5, CD19, CD20, CD22, CD23, CD200, and moderately dim monotypic immunoglobulin light chain lambda. This population comprised 96% of lymphocytes and was negative for CD10, CD11C, CD103, FMC7, and kappa light chain. Fluorescence in situ hybridization (FISH) testing was positive for 13q14.3 chromosome deletion, negative for trisomy 12, and negative for deletion of 6q, ATM, and TP53. The patient's heavy chain variable gene (IgV_H) was unmutated.

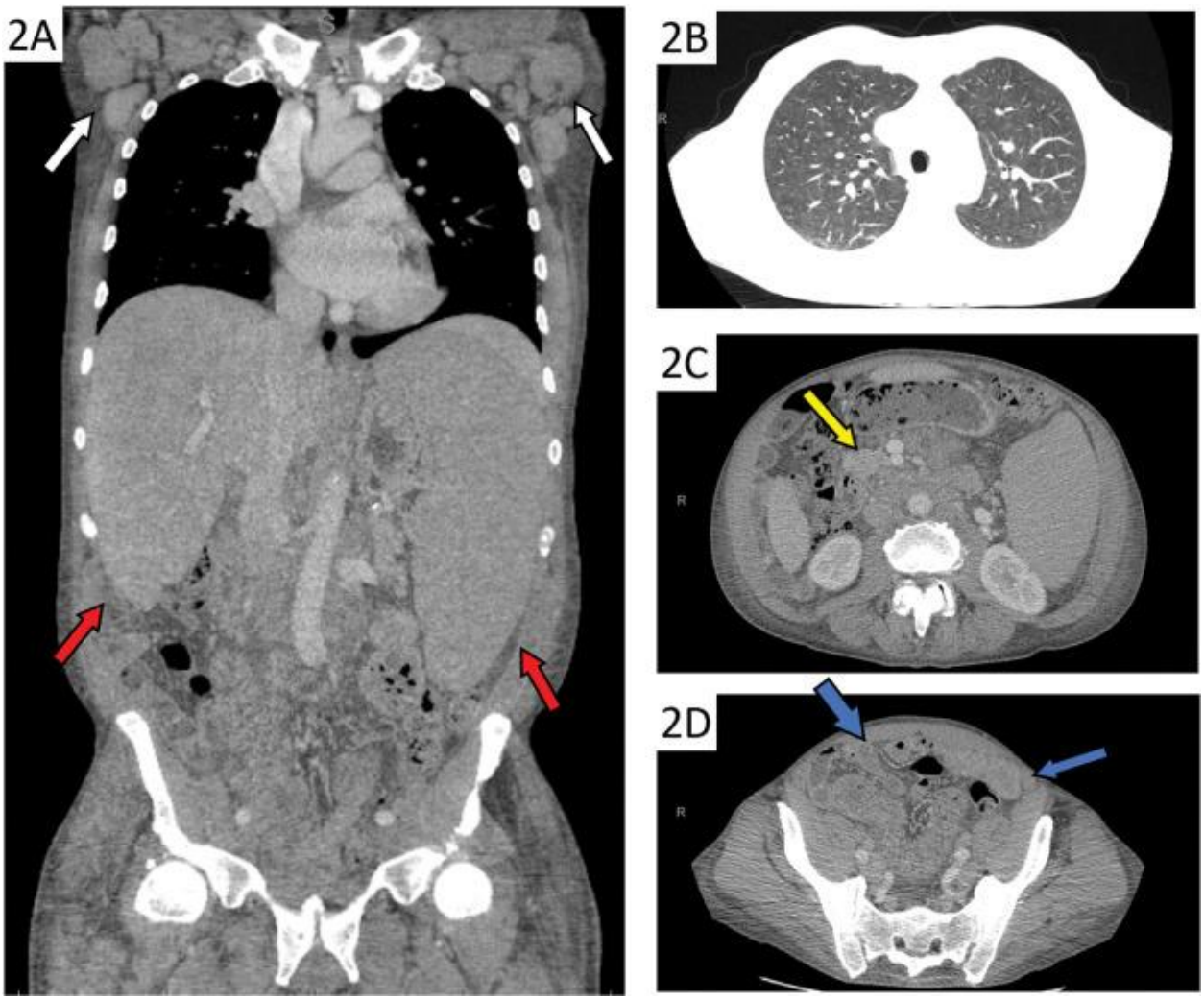

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Fig. 2

The patient was admitted to the hospital for treatment of retinal, pulmonary, and gastrointestinal leukostasis. He received normal saline at a rate of 100cc per hour and oral allopurinol 300 mg twice daily to minimize risk of tumor lysis syndrome (TLS) and in anticipation of CLL-directed treatment. The patient's hemoglobin declined on serial lab checks and a fecal occult blood test used to evaluate for gastrointestinal bleeding was positive. Subsequently, the patient received two units of irradiated and leukocyte-poor packed red blood cells (PRBCs) for active gastrointestinal bleeding. On hospital day three,

following his first leukapheresis session, he received a single 0.5 mg/kg dose of oral chlorambucil. After his second leukapheresis session, he began acalabrutinib at a dose of 100 mg twice daily. The next day he received a third and final cycle of leukapheresis. These interventions resulted in a reduction of WBC from 522.6 × 10_9/L to 231.8 × 10_9/L. By day four, his HCT drifted down to 21% thus requiring a third unit of PRBCs. On hospital day six, his platelet count fell to 19 × 10_9/L, and he received 1 unit of random donor platelets. The following day he received a fourth unit of PRBCs. Throughout the duration of his hospitalization, his electrolyte, uric acid, chemistry, and coagulation panels remained stable. On the eighth hospital day, he reported improvement in his vision and resolution of gastrointestinal and pulmonary symptoms. On the morning of discharge, the patient's WBC was 312 × 10_9/L, HCT was 27%, and platelet count was 32 × 10_9/L (Fig. 3A).

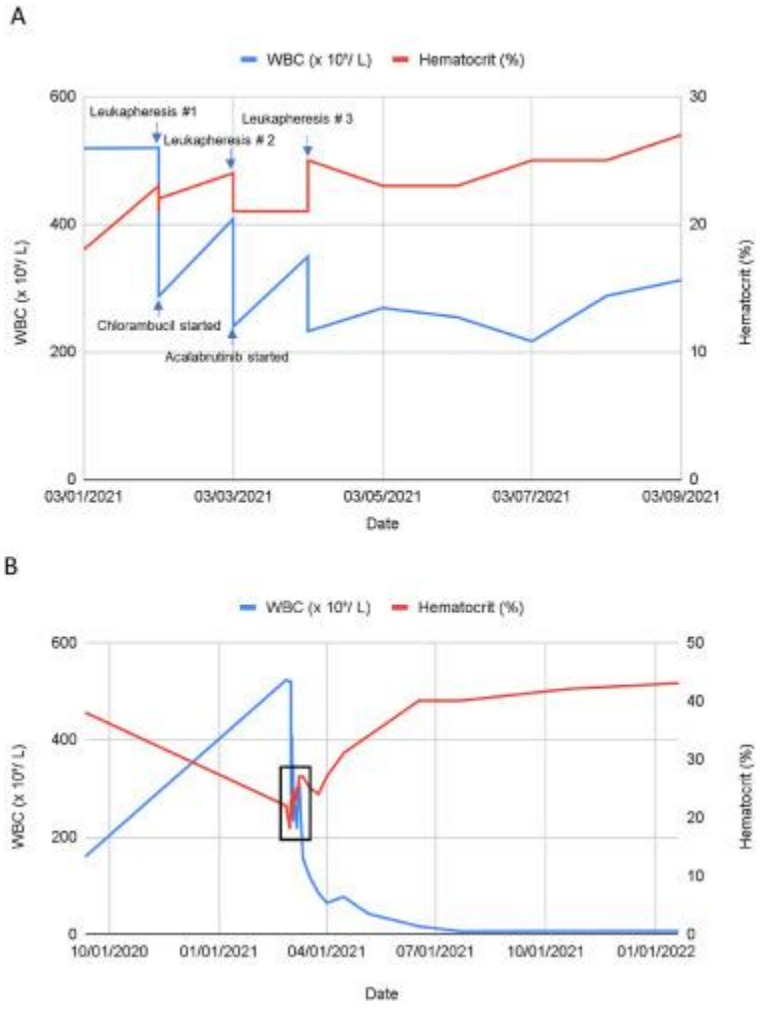

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Fig. 3

The patient was followed closely as an outpatient with physical examinations and serial blood tests. A chest radiograph four weeks after hospital discharge was unremarkable and a colonoscopy performed two months later was also normal. Over the following months his vision returned to normal, hepatosplenomegaly and lymphadenopathy resolved, and his aberrant laboratory values continued to improve (Fig. 3B).

At his most recent 12-month follow-up in our hematology clinic, the patient was feeling well and had no overt side effects from acalabrutinib. His physical exam was without pronounced lymphadenopathy or hepatosplenomegaly. His WBC was 6.4 × 10_9 /L, HCT was 43%, and platelet count was 103 × 10_9/L. Electrolytes, transaminases, and serum LDH were all within normal limits. He reported a persistent grayed-out spot in his left eye but noted overall improvement in his vision. His follow-up retinal exam was notable for central pigment in the fovea of the left eye with resolution of the previously visualized intraretinal hemorrhage. His left eye visual acuity had also improved to 20/40.

3. Discussion

Leukostasis syndrome is defined as hyperleukocytosis (WBC > 100 × 10_9/L) that is associated with symptoms related to pathological leukocyte aggregation. Patients with leukostasis syndrome commonly present with cardiopulmonary symptoms and neurologic deficits, which have been correlated with autopsy evidence of both direct tissue infiltration by leukemic cells and leukemic thrombi that cause vascular occlusion or hemorrhage (McKee and Collins, 1974).

Several theories have been proposed to explain the relative rarity of leukostasis in CLL (Rampling, 2003). Foremost among them is the premise that CLL cells have more favorable mechanical properties and adhesion

characteristics than those of other hematologic malignancies. Leukemic lymphocytes have a smaller cell volume (190 to 250 μm_3) compared to leukemic myeloblasts (350 to 450 μm_3), corresponding to a higher leukocrit for myeloid malignancies at a given leukocyte count (Lichtman and Rowe, 1982). This may explain why leukostasis in the case of CLL is most often seen when the WBC is greater than $500 \times 10_9/L$, which is considerably higher than in myeloid malignancies (Ganzel et al., 2012) where the WBC tends to be around $100 \times 10_9/L$. Hyperleukocytosis with a WBC greater than $100 \times 10_9/L$ is generally associated with a decrease in HCT resulting in a normal whole-blood viscosity in cases of CLL leukostasis (Lichtman and Rowe, 1982, Herman et al., 2014). This observation led to microrheological studies of abnormal leukocytes to better characterize cellular properties that influence microvascular flow. Leukemic cells, especially larger and stiffer myeloid blasts, can impair flow as they pass through small blood vessels (Lichtman and Rowe, 1982). This microvascular flow impairment is magnified by a high leukocrit and the increased oxygen consumption of leukemic cells, which more commonly occurs in myeloid leukemias versus lymphocytic leukemias (Rampling, 2003).

The microrheology theory does not adequately explain the observation that hyperleukocytosis alone does not always result in leukostasis syndrome, suggesting that there are molecular interactions that contribute to the development of leukostasis. Leukemic blasts from patients with acute myeloid leukemia (AML) secrete pro-inflammatory cytokines including IL-1β and TNF-α that promote adhesion of myeloblasts to the endothelium. In addition, mechanisms of tissue damage including cytokine and matrix metalloproteinase-mediated endothelial damage, as well as local hypoxia are associated with microhemorrhage and extravasation of leukemic cells into the interstitial space (Bewersdorf and Zeidan, 2020).

In contrast to other acute and chronic leukemias, CLL often has a benign clinical course and low-risk patients may be asymptomatic for years (International CLL-IPI Working Group 2016). Physical examination and standard laboratory tests, in addition to a multitude of prognostic biomarkers, are widely used to risk stratify patients (Binet et al., 1981). Patients with isolated lymphocytosis are considered low-risk and generally monitored

without treatment, though routine laboratory testing may reveal profound elevations in the WBC that often exceed 100 × 10_9/L. Treatment is indicated for patients with active disease as evidenced by development of CLL-related symptoms or progression of tumor burden. Examples of progressive disease include the development of constitutional symptoms, bone marrow failure, rapidly rising WBC, and progression of lymphadenopathy among other criteria developed by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) (Hallek et al., 2018).

The treatment of lymphocytic leukostasis centers around reducing the aberrant lymphocyte population. Historically, antilymphocyte treatment regimens utilized glucocorticoids and cytotoxic chemotherapy. Standard first-line therapies for CLL have included the fludarabine, cyclophosphamide, and rituximab (FCR) chemoimmunotherapy regimen (Shanafelt et al., 2019), bendamustine and rituximab (Ghia et al., 2020), and chlorambucil and Obinutuzumab (Sharman et al., 2020). In the past few years, CLL treatment has advanced considerably with the advent of targeted therapies that have supplanted chemoimmunotherapy (Patel and Pagel, 2021). The adoption of Bruton's tyrosine kinase (BTK) inhibitors including ibrutinib and acalabrutinib, in addition to the B-cell lymphoma 2 (BCL2) inhibitor venetoclax have dramatically changed the treatment paradigm for CLL (Jain, 2022), especially for patients with high-risk prognostic markers. These treatments have increased the life expectancy of high-risk patients from around two years with chlorambucil to more than five years with ibrutinib (Burger et al., 2020).

BTK inhibitors are highly effective but often cause redistribution lymphocytosis, which leads to a transient albeit sometimes extreme increase in WBC as the abnormal lymphocytes are mobilized from lymph nodes and other tissues into the peripheral blood (Choi et al., 2018). The onset and peak of treatment-induced lymphocytosis is highly variable but is more pronounced and slower to resolve in patients with IgVH-unmutated CLL (Herman et al., 2014). This lymphocytosis is typically asymptomatic and not associated with leukostasis syndrome based on several studies (Herman et al., 2014, Byrd et al., 2013), even though the WBC in some instances exceeded 600 × 10_9/L. Although there is no known precipitating factor for leukostasis syndrome in

CLL, an increasing WBC appears to correlate with an increased risk of developing leukostasis (Ali et al., 2016). Thus, it is standard practice to monitor these patients closely.

The role of chemoimmunotherapy is restricted to young (typically age less than 65 years) patients with CLL without significant comorbidities, who have a mutation in the immunoglobulin heavy chain but lack the del(17p)/TP53 mutation; this constitutes only about 10% of all patients with CLL requiring first-line therapy. For this patient population, treatment with the FCR regimen can lead to long-term disease-free survival in about 50%-55% of the patients (Shanafelt et al., 2019). Despite this, the use of chemotherapy has declined given the potential for toxicities including cytopenia, infection, and the risk of therapy-related myelodysplastic syndrome or AML (Benjamini et al., 2015).

TLS, previously uncommon in CLL patients treated with chemotherapy, has increased in frequency and severity with the use of more effective targeted therapies that rapidly decrease tumor burden (Cheson et al., 2017). Renal and metabolic complications of TLS can be mitigated with intravenous hydration, close monitoring of serum electrolytes, and prophylactic administration of allopurinol to reduce the future production of uric acid. Patients with high-risk features (Davidson et al., 2004) or severe TLS (Cheson et al., 2017, McBride et al., 2017) may benefit from rasburicase, a recombinant enzyme that rapidly degrades existing plasma uric acid. Another consideration for CLL patients with hyperleukocytosis is the management of anemia, which can be due to a variety of etiologies. Although our patient received a total of four units of PRBCs, it is worth noting that transfusion of blood products can increase the viscosity of blood and should be performed with caution (Hallek et al., 2008).

Leukapheresis as a treatment for leukostasis remains controversial; there is insufficient evidence of improved long-term survival in patients with AML (Connelly-Smith and Linenberger, 2020, Oberoi et al., 2014), which tends to be more aggressive than CLL. Several studies were unable to identify a significant difference in early mortality (Choi et al., 2018) or overall survival (Stahl et al., 2020) after adjusting for age and performance status in patients

with AML. Two retrospective meta-analyses analyzed the use of leukapheresis to treat leukostasis syndrome in AML; neither study found a significant difference in primary outcome of early mortality between leukapheresis and other treatments (Bewersdorf and Zeidan, 2020, Oberoi et al., 2014). Based on these findings, the American Society for Apheresis revised its guidelines to recommend leukapheresis only as a second-line therapy for AML patients with leukostasis (Padmanabhan et al., 2019) due to its high resource utilization and serious risks. Those who have traditionally been considered in need of the procedure often have thrombocytopenia and coagulopathy which complicate the placement of the large-bore temporary central venous catheter that is almost always required (Kalantari, 2012). Furthermore, the apheresis procedure itself can worsen existing coagulopathy by depleting platelets and consuming coagulation factors, particularly fibrinogen (Padmanabhan et al., 2019).

Despite its uncertain benefit, leukapheresis has been used as a prophylactic measure for treatment-induced leukocytosis to rapidly reduce the WBC in CLL patients without clinical leukostasis (Ganzel et al., 2012, Cunningham et al., 2015). A single leukapheresis treatment can decrease the WBC by 20-50%, which is critical in reversing tissue hypoxia, particularly in sensitive organs like the central nervous system (Ganzel et al., 2012). In contrast, induction chemotherapy can take hours to days before cytoreduction occurs (Bug et al., 2007). For our patient with multisystem leukostasis, we utilized leukapheresis in combination with pulse chlorambucil to mitigate the risk of acalabrutinib-induced leukocytosis. We decided against monoclonal antibody therapy to avoid the risk of further immunosuppression during the COVID-19 pandemic (Chatzikonstantinou et al., 2021) and venetoclax-based therapy to avoid precipitating TLS (Brem and O'Brien, 2022).

There is insufficient data and limited society guidance on the management of CLL patients with extremely high baseline leukocyte count or clinical leukostasis. To better understand the clinical presentation and laboratory variables of patients with CLL and leukostasis syndrome, as well as the reported benefits of leukapheresis, we performed a literature review. We also looked to see if there was an association between leukostasis syndrome and treatment-associated leukocytosis. We interrogated Embase, PubMed, and

ClinicalKey databases using the following search terms: leukemia, lymphocytic, chronic, patient outcomes, leukostasis, and outcome assessment. Additional searches were performed using the Medical Subject Headings (MeSH) “B-cell”, “Leukostasis” and the Emtree subject heading “chronic lymphocytic leukemia.”

Including our patient, we identified 16 cases that were published in English or had an available full text English translation (Table 1). The median patient age was 71 years (range, 48-89) and 11 (73%) were males. Twelve out of 16 patients (75%) survived hospitalization, 3 patients (19%) died during hospitalization, and 1 patient (6%) died at home prior to reassessment. The median WBC was 389.9 × 10_9/L (range, 117 to 2000 × 10_9/L). Pulmonary leukostasis was reported in 13 cases (81%) as a primary or secondary diagnosis and neurologic symptoms were reported in 3 cases. Large intravascular leukocyte thrombi involving major blood vessels or heart chambers were reported in 4 cases (27%) (Beaubien et al., 1998, Cukierman et al., 2002, D'Angelo et al., 2000, Kumar and Sadaka, 2021). Signs and symptoms, especially those from neurologic deficits, were reported to improve shortly after completion of leukapheresis. The most common terminal complications of leukostasis were cardiopulmonary arrest and multisystem organ failure (Beaubien et al., 1998, Gitto et al., 2021, Hosseinnezhad et al., 2011, Singh et al., 2020). Leukapheresis was successfully used as monotherapy in only one instance where the patient declined chemotherapy but agreed to undergo leukapheresis (Karaman et al., 2020). This resulted in resolution of pulmonary infiltrates on CT imaging and corresponded to improvement in the patient's pulmonary symptoms. The patient felt sufficiently well to return home, but his WBC after leukapheresis and long-term outcomes were not reported. In our case as well as several others, leukapheresis was used sequentially with other treatments (Cukierman et al., 2002, Singh et al., 2020, Karaman et al., 2020, Atwal et al., 2017, Ibrahim et al., 2019) which confounds our interpretation of reported outcomes.

Abbreviations: BAL, bronchoalveolar lavage; DVT, deep vein thrombosis; F, female; FCR, fludarabine, cyclophosphamide and rituximab; HCT, hematocrit; Hgb, hemoglobin; IVIG, intravenous immune globulin; M, male; TLS, tumor lysis syndrome.

In our literature review, complications associated with leukapheresis were infrequently reported. Leukapheresis was discontinued prematurely due to hypotension in one case (Ibrahim et al., 2019) and the patient died shortly thereafter from multisystem organ failure. Another patient developed a central venous catheter-associated thrombus (Atwal et al., 2017), which is a known complication of the vascular access required for leukapheresis (Ganzel et al., 2012). Despite this, he responded well to treatment and survived hospitalization. Overall, patients tolerated chemotherapy and leukapheresis even when complications developed (Singh et al., 2020, Atwal et al., 2017) and despite initial WBC greater than $1000 \times 10_9/L$ (Cukierman et al., 2002, Atwal et al., 2017, Awad et al., 2015). In the other four instances where the patient died prior to or during hospitalization, the ultimate cause of death was attributable to refusal of standard treatments (Beaubien et al., 1998), poor baseline health (Gitto et al., 2021, Hosseinnezhad et al., 2011) or treatment failure with relapsed disease (Ibrahim et al., 2019). One patient with severe chronic obstructive pulmonary disease (Hosseinnezhad et al., 2011) opted for comfort measures after his pulmonary leukostasis worsened despite treatment with chlorambucil.

Limitations of our review include the extreme rarity of this condition, incomplete reports on treatments and outcomes, and heterogeneity in patient age and medical comorbidities. In addition, these cases were described in the backdrop of outmoded chemoimmunotherapy that does not reflect the improved options currently available for CLL patients. Patients with complaints of shortness of breath with pulmonary infiltrates on imaging were often started on empiric antibiotics to treat presumed sepsis prior to the diagnosis of leukostasis. Most studies combined leukapheresis with antilymphocyte medications, and there were no published studies that compared the outcomes of leukapheresis versus pharmacologic cytoreduction alone.

4. Conclusion

As BTK inhibitors and other breakthrough CLL treatments that are known to induce leukocytosis continue to supplant traditional treatments, the incidence of hyperleukocytosis is expected to rise. Leukapheresis can be used in

conjunction with other cytoreductive strategies in select situations to rapidly reduce the WBC, improve neurologic symptoms, and mitigate the effects of treatment-induced hyperleukocytosis. Further studies are needed to identify whether treatment-induced hyperleukocytosis can exacerbate existing leukostasis. It is also important to further characterize the risk-benefit ratio, and longer-term outcomes of leukapheresis versus pharmacologic cytoreduction alone, especially in patients with high-risk CLL subtypes and favorable functional status.