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A Rare Presentation of Neutrophilic Eccrine Hidradenitis in the Management of Acute Myeloid Leukaemia: A Case Report

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Abstract

We present an unusual case of a 62-year-old male who was diagnosed with acute myeloid leukaemia and developed bilateral periocular skin dermatosis, concerning for neutrophilic eccrine hidradenitis, after receiving induction chemotherapy with Idarubicin and Cytarabine. On day seven of induction therapy, the patient developed swelling and discomfort around his right eye, which quickly progressed to involve the left side. Patient improved with supportive care with topical steroids and anti-inflammatory medications. Neutrophilic eccrine hidradenitis is typically a self-limited process. It does not appear to be associated with a worse prognosis for the underlying malignancy when occurring in that setting. The purpose of this report is to bring to light the importance of having a broad differential for dermal lesions in neutropenic patients and the avoidance of inappropriate therapy to prevent subsequent adverse events.

Keywords: Acute myeloid leukemia; Idarubicin; Cytarabine; Neutropenia; Neutrophilic eccrine hidradenitis

Introduction

Neutrophilic Eccrine Hidradenitis (NEH), also known as chemotherapy-associated eccrine hidradenitis, is an uncommon dermatosis which is attributed to chemotherapy drugs in the setting of neutropenia in patients with solid and hematologic malignancies [1]. NEH is more frequently reported in patients with acute myeloid leukemia who are being treated with cytarabine; but more recently, it has also been associated with carbamazepine and other newer anti-neoplastic agents [2].

The clinical lesions are typically erythematous and edematous plaques which can be purpuric and painful. They are usually located on the extremities, trunk, face, and palms, and may mimic cellulitis when appearing around the eyes. A skin biopsy demonstrating typical pathologic changes of the eccrine glands is required to confirm a diagnosis of NEH. It is characterized by a neutrophilic infiltrate around the eccrine glands and coils and is associated with necrosis [3]. Treatment is supportive and mainly involves topical or systemic corticosteroids and anti-inflammatory drugs.

We report an unusual case of a leukemia patient experiencing periocular skin manifestations concerning for NEH after receiving induction chemotherapy with idarubicin and cytarabine.

Case Presentation

A 62-year-old male with history of hypertension, gout and gastroesophageal reflux disease presented to an outside facility with a two-week history of severe fatigue, shortness of breath, 15-pound weight loss and night sweats. On further history, he reported having intermittent fatigue, and headache for the past 2 years. Physical examination was remarkable for a large ecchymosis noted on right upper extremity along with reduced sensation to light touch on left lower extremity up to the level of knee. Initial blood work showed hemoglobin: 9.4 g/dl, white blood cell count: 52 K/mm^3 with a predominance of blasts, platelet count: 23 K/mm^3, lactate dehydrogenase: 1096 U/L, uric acid: 7.6 mg/dL. Peripheral smear is remarkable for 61% blasts. Bone marrow biopsy performed at outside facility was consistent with acute myeloid leukemia and hence patient was transferred to our facility for higher level of care.

Patient was started on all-trans retinoic acid (ATRA) on admission due to concerns of acute promyelocytic leukemia (APML) along with hydroxyurea. Flow cytometry results on peripheral blood showed blasts expressing CD13, CD33, and HLA-DR; a minority expressed CD4, CD11b and CD117. FISH testing for PML-RARA was negative the next day and ATRA was stopped. Induction chemotherapy with idarubicin and cytarabine was started. Lumbar puncture was performed once peripheral white blood cell count was reduced to less than 10 K/mm^3 and there was no evidence of leukemic cells in cerebrospinal fluid.

On day seven of induction therapy, the patient developed swelling and discomfort around his right eye, which quickly progressed to involve the left side. The patient denied any associated vision changes, pain on extraocular movements, foreign body sensation, or photophobia. He had no other systemic complaints and vitals were within normal limits. Physical examination was remarkable for bilateral periocular erythematous and edematous maculopapular lesions (Figure 1). There was no evidence of conjunctival injection, tenderness, or purulent discharge. Visual acuity was preserved and fundoscopy did not reveal any abnormalities in both eyes. Patient was

clinically doing well with no reported fever or rash anywhere else. Laboratory results were significant for pancytopenia with absolute neutrophil count: 0.04 k/mm^3, hemoglobin: 8.1 g/dl, platelet count: 10,000 k/mm^3. We had a broad differential diagnosis including, but not limited to leukemia cutis, myeloid sarcoma, neutrophilic eccrine hidradenitis, sweet's syndrome, *Pyoderma gangrenosum*, cellulitis, and infectious eccrine hidradenitis. Computerized tomography showed pre-septal and periorbital edema without evidence of abscess or orbital mass. Biopsy of the lesion could not be performed due to severe neutropenia.

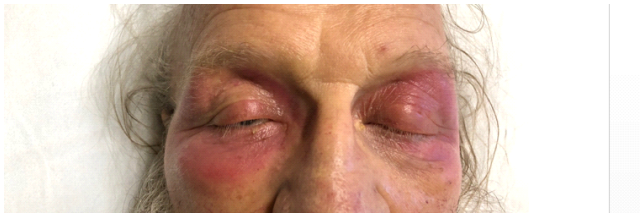

Figure 1: Bilateral periocular erythematous and edematous maculo-papular lesions.

Due to the presence of characteristic skin lesions for NEH, no evidence of infection on CT imaging, and the plausible temporal relationship with recent cytarabine exposure, we narrowed our differential to NEH. Topical steroids and anti-inflammatories were used. Periocular lesions began to show improvement within 5-7 days and completely resolved with supportive care within 2 weeks. While faced with diagnostic certainty without tissue biopsy, the overall clinical picture and its spontaneous resolution without antimicrobials was suggestive of NEH. Patient had a day 28 bone-marrow aspirate and a biopsy which showed 1% blasts and he was subsequently discharged with a plan to start consolidation chemotherapy.

Discussion

Neutrophilic Eccrine Hidradenitis (NEH), also known as chemotherapy-associated eccrine hidradenitis, is an uncommon dermatosis which is attributed to chemotherapy drugs in the setting of neutropenia in patients with solid and hematologic malignancies [1]. A meta-analysis conducted by Bachmayer identified a slight male predominance for NEH while no sex predilection for acute myeloid leukemia exists. It has been reported to affect individuals as young as six months and as old as 79 years, in the literature. The mean age of presentation was 40 years [4]. NEH may occur in children during summer season without any association with a disease or a medication, secondary to thermal damage of eccrine glands [5].

Causative agents include granulocyte colony-stimulating factors, cyclophosphamide, cytarabine, methotrexate, carbamazepine, bleomycin, methotrexate, 5-fluorouracil, and antiretroviral medications. More recently, NEH has been shown to be associated with hypomethylating agents like decitabine [6] and targeted agents like BRAF inhibitors, dabrafenib [7] and epidermal growth factor inhibitor, cetuximab [8]. However, cytarabine and anthracyclines are the more common offenders [9]. It is reported that more than 70% of patients with malignancies who develop NEH, do so after their first course of chemotherapy [10].

While the exact mechanism is unclear, the most likely mechanism of injury is due to direct cytotoxic effect of the offending agent to rapidly dividing cells in the skin. Another proposed mechanism of injury is a primary neutrophilic response to the causative drug or malignancy [1]. Another hypothesis describes NEH as a part of the neutrophilic dermatoses spectrum and as a paraneoplastic condition [11]. As NEH has also been described in a healthy population therefore a possibility of underlying sweat gland abnormalities has also been suggested.

The clinical picture includes erythematous papules, nodules or plaques over the skin, and is commonly accompanied by fevers. The skin lesions of NEH are protean and usually favor the trunk and less commonly involve face, periocular sites, and extremities. Lesions are typically seen to originate within two to three weeks after initiating the offending agent. The lesions may or may not have central necrosis. To the best of our knowledge, very few cases of neutrophilic eccrine hidradenitis involving periocular regions have been reported [12-15]. The differential diagnosis includes infectious and inflammatory etiologies including leukemia cutis, myeloid sarcoma, cutaneous tumor metastasis, erythema multiforme, vasculitis, drug hypersensitivity, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), sweet syndrome and *Pyoderma gangrenosum*. The diagnosis of NEH can only be ascertained with means of histological evaluation which usually reveals neutrophilic infiltration and necrosis of the eccrine glands along with degenerative vacuolar changes [1]. Harrist et al. described that the robust neutrophilic infiltrate is classic for diagnosis, but it is not required [16]. In patients with chemotherapy-induced neutropenia, neutrophils can be absent on histopathologic examination [17].

It can be difficult to clinically differentiate NEH from cellulitis though cellulitis is mostly tender, warm and has irregular margins. Micro-organisms have also been implicated in the etiology of NEH in some case reports, including human immunodeficiency virus, gram-positive cocci, *Streptoccoccus* species, *Serratia marescens*, *Nocardia* species, *Enterobacter cloacae* and *Staphyloccocus aureus* [13]. Whenever there is a clinical suspicion, it is recommended to perform special stains and tissue cultures to look for infectious agents [4]. Our patient was afebrile with no clinical suspicion of infection during this course and hence additional work up was not performed.

NEH resolves spontaneously within a few days to weeks after discontinuing chemotherapy. However, it can recur with subsequent treatment cycles [18]. Treatment is supportive and mainly involves topical or systemic corticosteroids and anti-inflammatory medications [13], although the available evidence is limited to descriptive studies (level III). Nonsteroidal anti-inflammatory drugs and systemic steroids have shown efficacy in literature in reducing pain and controlling fever in patients with NEH [18].

Nonetheless, corticosteroids should be used with caution in neutropenic patients. Pain should be managed with analgesic medications if tender lesions are present. One study reported use of colchicine in a healthy patient with histological diagnosis of NEH whose lesions improved after one month of therapy [19]. Our patient demonstrated clinical features consistent with NEH. Inability to perform a biopsy of the suspected lesions to confirm the diagnosis is a limitation. Severe neutropenia precluded us from obtaining a biopsy of the affected periocular area. However, the time of onset after cytarabine therapy and spontaneous resolution of the skin lesions without the use of anti-microbial therapy makes us almost certain of the diagnosis of NEH.

It is reported in literature that some patients experience recurrences of the cutaneous eruptions upon reintroduction of chemotherapeutic

regimens. There have been case reports describing the use of dapsone as prophylaxis to minimize the incidence of NEH. Dapsone 100 mg daily was started 48 h before chemotherapy and continued for 14 days in these reports and has been proposed as a successful regimen for preventing NEH in patients undergoing chemotherapy. The mechanism is believed to be due to the inhibitory effect of dapsone on neutrophilic migration [20]. The possible hematologic toxicity associated with dapsone in the setting of chemotherapy regimens needs to be considered prior to initiation of prophylaxis.

The purpose of this case report is to bring to light the importance of having a broad differential for dermal lesions in neutropenic patients and the avoidance of inappropriate therapy to prevent subsequent adverse events.

Conclusion

We have reported an unusual presentation of a patient undergoing chemotherapy for acute myelogenous leukemia, who presented with classic NEH lesions in periocular region. To the best of our knowledge, very few cases have been reported in literature so far. The differential diagnosis is broad, ranging from infectious and inflammatory etiologies including leukemia cutis, myeloid sarcoma, cutaneous tumor metastasis, erythema multiforme, vasculitis, drug hypersensitivity reaction, sweet syndrome and *Pyoderma gangrenosum*. NEH is commonly seen in patients on active chemotherapy, and lesions can present sometimes during neutropenic phase. In our case, cytarabine was the most likely etiology for NEH. In cases where risks of biopsying the skin lesions outweigh the benefits, similar to the patient we described in our case report, we recommend continuing with supportive care. We emphasize the necessity of a prompt diagnosis in order to prevent the use of inappropriate therapy.

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