Erythromelalgia, where is it coming from?

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GRADUATE MEDICAL EDUCATION

Learning Objectives:

1. Presentation and physical findings
2. Pathophysiology
3. Diagnosis
4. Medical Management

Clinical Overview:

- **Physical Presentation:** Erythromelalgia (EM) is a rare clinical presentation characterized by attacks of severe burning, erythema, and warmth of the extremities of the body.
- **Pathophysiology:** The primary EM is caused by a mutation in the SCN9A gene, which increases the perception of pain. On the other hand, the secondary form is triggered by wide extensive pre-existing conditions[1]. The possible explanation of the symptoms is the maldistribution of the available perfusion in favor of arteriovenous (AV) anastomoses shunting with subsequent hypoxia in the acral areas. [2]
- **Infrequently:** EM on a setting of ET and dermatomyositis (DM) is not reported in the literature.
- **Condition associated:** connective tissue disorders, myeloproliferative disease such as polycythemia vera (PV) or essential thromcytosis (ET), and inflammatory diseases
- **Management:** crucial to distinguish between primary and secondary condition. For primary there is not cure but can control with life-style modification such as avoidance of precipitating factors, exposure of cool water in the affected area, limb elevation, some case series report symptom improvement with lidocaine, diclofenac 1% gel, or systemic treatment with aspirin (3-4). For secondary EM is controlling the underlying cause.

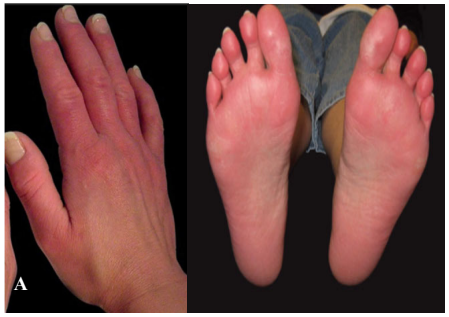

Figure 1. A. Appreciate right dorsal erythema that start in fingers and extend to metacarpophalangeal (MCP) joints. B. Bilateral erythema in the plantar area.

Clinical Case:

A 65-year-old Caucasia male presented at the clinic with three months history of bilateral pain in his hands. The patient described that he had soreness at the base of the nail beds and started to have morning muscle pain that lasted throughout the day without improvement. The patient also endorsed feeling tired during exercise after having pain in the hands and nail bed soreness and noticed erythema on his hands and feet.

Clinical assessment:

ROS:
Positive: erythema hands and feet, burning sensation, fatigue, proximal muscle pain, stiffness of metacarpophalangeal (MCP)
Negative: vision change, oral and mucosa change, skin or scalp change, weight loss, fever, and diaphoresis at night
Differential diagnosis: erythromelalgia, enthesitis, dactylitis, lupus, and spondyloarthropathies

Laboratory:

Laboratory	Values	Reference
Hemoglobin	18.2 g/dL	14-18 g/dL
Hematocrite	57.7 %	42-52 %
Mean corpuscular volume (MCV)	83.5 fL	80-90 fL
Platelet	557 K/uL	130-400 K/uL
Erythropoietin (EPO)	2.5 mIU/mL	2.6-18.5 mIU/mL
Creatinine	0.89 mg/dL	0.80-1.3 mg/dL
C- reactive protein	1.45 mg/dL	0.0-0.6 mg/dL
Antinuclear antibody (ANA) Pattern	Speckled pattern	Negative
ANA titer	1:320	<1:160
Anti-dsDNA (Anti-double stranded DNA)	0 IU/ml	0-80 U/ml
TSH (thyroid-stimulating hormone)	1.680 IU/ml	0.350-4.940 IU/ml

Table 2

Laboratory	Values	Reference
Anti P155/140 Antibody	Positive	Negative
Anti transciptional intermediary factor - 1B (TIF-1γ)	Low positive	Negative
Janus kinase (JAK2 V617F) mutation	Detected	Negative
Creatinine phosphokinase (CPK)	15	10-120 mcg/L
Anti-JO1	Negative	Negative

Table 2

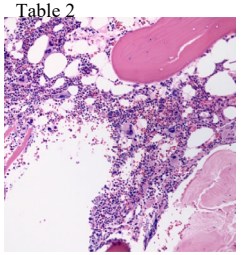

Figure 2. A. Bone marrow biopsy showing atypical megakaryocytes with atypical megakaryocytes, which are enlarged, mature with hyperlobulated nuclei.

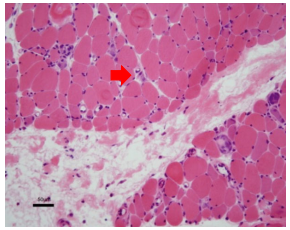

Figure 3. perivascular and perimysial inflammation (red arrow) and perifascicular atrophy

Clinical course:

•The patient was seen by an Oncologist who ordered EPO test and iron panel, which both were negative. JAK2 V617F mutation was sent, and it was positive (Table 2). Peripheral blood smear showed mild polycythemia with normochromic, normocytic red blood cells, thrombocytosis with increased large platelet forms without sign of blast cells.

•Bone marrow was performed and showed megakaryocytes, distributed in clusters, hyperlobated nuclei with CD31 positive. The final report was JAK2 positive myeloproliferative fibrosis with essential thrombocytosis (ET). The patient was started on 500 mg of hydroxyurea with aspirin 81 mg daily. The plan was a weekly check of hematocrit with phlebotomy as needed with a goal of < 45%.

•Due to a positive ANA test, the patient was sent to the rheumatologist, and the patient-reported upper and lower extremity weakness. The patient endorsed difficulty raising his arms above his neck. With the concern of possible DM or polymyositis (PM), an autoantibody test was sent.

•The patient underwent punch biopsy in the dorsal thumb, and the report showed perivascular and perimysial inflammation and perifascicular consistent with DM. The patient was started on methotrexate.

•Subsequently, the patient developed dysphagia for solid and liquid and was sent to a gastroenterologist who performed endoscopy with Barrett's stage C1-M2 and esophageal candidiasis. The patient started on fluconazole oral 200 mg daily.

•Due to concern of paraneoplastic rheumatic disease with positive Anti-P155/140 and TIF-1γ, the patient underwent computerized tomography of the chest (CT) and positron emission tomography, both negative.

Learning Points & Discussion:

➢DM, PM, necrotizing myopathy (NM), and inclusion body myositis (IBM) can present as cancer associated myopathy (CAM). [4]

➢DM and PM were two of the more common presentations - the incidence of DM as a CAM was 20.5% (30 out of 146 patients) while the incidence of PM was 4.3% (13 out of 304 patients). [5]

➢The histopathology of DM is predominantly inflammatory infiltration at perivascular sites or within the interfascicular septae.

➢The main pathological characteristic is the distribution of atrophic, degenerating, and regenerating fibers at the periphery of the fascicle, and perifascicular atrophy involving both type 1 and type 2 muscle fibers, which may affect two to ten layers.[6]

➢DM associated cancer are:

➢Breast cancer, lung, ovary, stomach, intestine, nasal cavity, throat, pancreatic, bladder, and Hodgkin's lymphoma

➢Anti-p155 is a myositis-specific antibody that was recently discovered and is reactive against the transcription intermediary factor-1gamma (TIF-1γ) protein, involved in cell proliferation, immunity, and carcinogenesis. Anti-p155 is highly associated with CAM and its presence is associated with a 27-fold increased chance of developing cancer compared with its absence[7]

Discusion:

Erythromelalgia is a rare clinical presentation and it is important to rule out secondary causes. Therefore, it is important to have a broad differential diagnosis

In our case, ordering auntoimmune workup helped to refer the patient to a rheumatologist which was essential in our patient

With antiP155/140 positive is important to search for neoplastic disease and do a thorough workup

Our case was negative for solid cancer and Hodgkin lymphoma. It is possible that ET was the cause of DM. If this is true, this is the first case report that present DM as CAM secondary to ET. We believe that JAK2 V617F may contribute with the development of DM, but further research are necessary

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