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Case Report

Raynaud's Phenomenon as the Initial and Only Manifestation of Non-Hodgkin Lymphoma: A Case Report

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ABSTRACT

Raynaud's phenomenon is one of the commonest manifestations of rheumatic diseases. However, it can be caused by non-Rheumatic conditions as well. Among non-rheumatic causes, cancers are widely reported as the culprit". Raynaud's phenomenon caused by non-rheumatic diseases are commonly resistant to standard treatment options They are associated with more severe infections. Among non-rheumatic causes, cancers are widely reported as the culprit. We present a case of non-Hodgkin lymphoma presenting solely with Raynaud's phenomenon.

INTRODUCTION

Raynaud's phenomenon is a characteristic and significant feature of connective tissue diseases such as Scleroderma, mixed connective tissue disease (MCTD), Sjogren syndrome, and systemic lupus erythematosus [1]. It is characterized by increased sensitivity of digital blood vessels, cold temperatures, and surge in catecholamines. This condition manifests clinically as a painful color change in fingers from pinkish white to white, blue and red which indicates ischemia, increased deoxyhemoglobin in blood vessels, and reactive hyperemia [2]. Laboratory and radiological tests help to exclude or confirm other conditions such as anti-phospholipid syndrome, cancers, vasculitis.

In rare cases, Raynaud's is associated with increased catecholamine release such as epinephrine and norepinephrine in certain neuroendocrine tumors and lymphomas. Non-Hodgkin lymphoma (NHL) is a neoplasm that develops from B cell precursors, mature B cells, T cell progenitors, and mature T cells. The clinical symptoms of NHL depend on the disease's stage; the common ones are lymphadenopathy, fever, weight loss, and organomegaly such as hepatomegaly and splenomegaly. Additionally, depending on the location affected by the disease, the symptoms could vary; for instance, diarrhea, abdominal pain in case of intestinal lymphoma, stroke, and seizures in case of central nervous system (CNS) lymphoma [3]. In neuroendocrine locations, the disease can be represented by increased catecholamine surge, diarrhea, high blood pressure, headache, sweating, flushing, etc. The case presented here is a non-Hodgkin lymphoma in its initial stage represented by severe Raynaud's phenomenon. Through this, we aim to offer information regarding diagnostic workup, treatment and refractory management protocol.

CASE PRESENTATION

An 18-year-old male presented to the rheumatology outpatient department with complaints of nonhealing ulcers on the

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Table 1. Laboratory features of the case

Characteristic	Reference value	UNIT	No:
Hemoglobin	13 - 18	g/dL	10.6
Total leukocyte counts	4-11	x10^9/l	8
Neutrophil	40.0-75.0	%	
Lymphocyte	20.0-50.0	%	
Eosinophils	1.0-6.0	%	
Platelets	15 - 400	x10^9/l	
ESR	≤15 mm/hr		32
C Reactive Protein	<10 mg/L		8
Albumin	3.50 - 5.20		4.2
Alanine Transaminase	UPTO 45.00	U/L	34
Aspartate Transaminase	UPTO 35.00	U/L	38
Thyroid Stimulating Hormone	0.45 - 4.5	(mU/L)	2.3
Hemoglobin A1C			4.5
Fasting lipid Profile			
HDL	>60	mg/dl	40
LDL	<130	mg/dl	80
Triglycerides	<150	mg/dl	140
Total cholesterol	<200	mg/dl	160
Anti - CCP antibodies	<20	EU/ml	Negative
Anti-Nuclear antibodies			Low titer positive,1:80 dilution
Extractable nuclear antigen (+ only)			Anti-MI 2 antibodies
Anti-neutrophilic cytoplasmic antibodies			negative

extensor surface of both elbows and painful bluish discoloration of fingers and toes. Discoloration was prominent on exposure to cold stimulus. The discoloration was episodic, painful, and had a characteristic three-phase change; from red to white, blue, and red again. The patient did not have any complains of weight loss, fever, night sweats.

The patient has a history of rhinosinusitis in the last two years with episodic epistaxis. It was attributed to the deviated nasal septum and managed conservatively. The systemic review was negative for any complains regarding anxiety, syncope, trouble breathing, trouble swallowing, diarrhea, joint pains. The patient had no weight loss, fever, or anorexia. Family history was insignificant. The patient had no history of drug or alcohol addiction, Vital signs were normal. Patient's cardiovascular, respiratory, abdominal and neurological examination was normal.

The patient had ongoing bluish discoloration in multiple digits (fingers and toes) and nonhealing second-degree ulcers on the extensor surface of the bilateral elbows at the time of examination. Peripheral pulses were palpable. The volume and character of pulse was normal. Workup was negative for anti-nuclear antibodies (ANA) and anti-neutrophilic cytoplasmic antibodies (ANCA). The extractable nucleic acid antigen panel through Quantrix (ENA) was positive for anti-M2 antibodies. Hepatitis B, hepatitis C, and Human Immunodeficiency Virus (HIV) were all negative, inflammatory markers (ESR, CRP), fasting lipids profile, blood sugar, renal function tests, liver function tests, and thyroid profile were all normal. A high-resolution CT scan (HRCT) chest showed bilateral ground glass opacifications with some nodularity.

The patient was started on vasodilators and immunosuppressants and labelled a case of seronegative ANCA vasculitis. The provisional diagnosis was made on the basis of respiratory involvement, presence of bluish discoloration and exclusion of other causes.

The patient received high dose oral prednisolone (40 mg per day for 1 month and then gradual tapered) and cyclophosphamide as per cyclops Trial (15 mg/kg IV cyclophosphamide fortnightly for three doses and thrice weekly for another three doses), along with dual coverage of vasodilators including calcium channel blockers and phosphodiesterase inhibitors (oral sildenafil). Mild improvement was noticed after three months of treatment. Patient reported flares of bluish discoloration and stiffness from time to time. No additional symptoms were accounted yet, his upper respiratory symptoms had improved.

Patient reported for a follow-up after 6 months. The patient returned with severe pain and impending gangrene of lateral 3 fingers of the right hand. There were no additional symptoms, laboratory workup was normal, and ANCAs were negative. The patient was admitted for other possible causes of illness. His CT scan thorax and abdomen with IV contrast showed lymph node enlargement in the neck, on both sides of the diaphragm, right adrenal mass, and splenomegaly. The patient underwent a cervical lymph node biopsy, which showed a reactive lymphocytic picture. Second laparoscopic

biopsy of adrenal mass showed diffuse large B-cell non-Hodgkin lymphoma. His PET Scan showed mucosal thickening noted in para nasal sinuses, likely inflammatory in nature; high metabolic activity in lymph nodes both above and below the diaphragm; and right adrenal mass consistent with the diagnosis of lymphoma. The patient was started on chemotherapy comprising of Rituximab, CYCLOPHOSPHAMIDE, Hydroxyrubicin, Vincristine, and methylprednisolone (also known as R-CHOP regime) by the oncology team. On follow-up, the patient's symptoms significantly reduced. Patient's symptoms kept on recurring despite optimum dose of calcium channel blockers.

DISCUSSION

Raynaud's phenomenon is fascinating for Rheumatologists due to its widespread autoimmune causes and a range of treatment modalities that come under the domain of Rheumatology. At present, the reflex workup and management plan for diagnosis are readily carried out, which generally helps identify the disease. However, Rheumatic diseases are not always the culprits. At times, Raynaud's is caused by diseases such as different types of malignancies, which occur either as a paraneoplastic syndrome or involvement of a neuroendocrine organ by the tumor. This could lead to increased sympathetic outbursts causing peripheral vasospasm [4,5]. Multiple reports have previously notified different types of malignancies causing Raynaud's phenomenon as the initial manifestation [6]. Most of such cases are either associated with other symptoms, which are not related to any Rheumatic disease, or the disease is refractory to treatment with conventional measures and drugs [7]. In this case, the diagnostic dilemma occurred due to the absence of such non-rheumatic manifestations that could lead to an alternate diagnosis and the presence of symptoms that could be easily contributed by Rheumatic diseases, such as upper respiratory tract involvement, etc.

CONCLUSIONS

We have described a unique multifocal extra-nodal DLBCL that affected many anatomical locations such as the head, thorax, lungs, liver, spleen, and abdomen. A PET/CT scan can detect and describe this unusual multifocal extra-nodal DLBCL presentation in great detail, as well as measure the severity of the disease's involvement and the treatment's effectiveness. However, a biopsy or surgical procedure is necessary to diagnose DLBCL. Although radiation and chemotherapy are administered as treatments, the prognosis may be at insufficient levels. Thus, it isn't easy to choose the best treatment plan; further study is needed.

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