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Blue toe syndrome as the initial manifestation of ANCA-associated vasculitis

Case Report

Liubomir M. Marinchev[1], Maria H. Hristova[2], Marta P. Baleva[2]*, Zlatimir G. Kolarov[1]

1 Clinic of Rheumatology, University Hospital St.Ivan Rilsky, Sofia, Bulgaria

2 Department of Clinical Immunology, University Hospital Alexandrovska, 1.G. Sofiiski Str., Sofia 1431, Bulgaria

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Abstract: The blue (or purple) toe syndrome describes the development of a blue or violaceous discoloration in one or more toes in the absence of obvious trauma, serious cold-induced injury or disorders producing generalized cyanosis. The presence of blue toe syndrome requires the clinician to search for primary systemic vasculitides, as well as for malignancy, underlying infection, thrombosis, cardiovascular pathology and other diseases. An accurate diagnosis is critical because many of the causes threaten life or limb, but the patient's medical history, accompanying non-dermatologic findings on physical examination and the use of discriminatory laboratory tests are usually more important than the nature of the cutaneous abnormalities. We describe the case of a 53-year-old Caucasian male patient presenting with blue toe syndrome as the initial manifestation of ANCA-associated vasculitis.

Keywords: *Blue toe syndrome • ANCA-associated vasculitis*

1. Introduction

The blue (or purple) toe syndrome described the development of a blue or violaceous discoloration in one or more toes in the absence of obvious trauma, serious cold-induced injury or disorders producing generalized cyanosis. The major causative categories are: (1) decreased arterial flow; (2) impaired venous outflow; and (3) abnormal circulating blood. Blue toe syndrome is occasionally seen in ANCA-associated vasculitides (AAVs). More often, the skin manifestations of AAVs include subcutaneous nodules similar to rheumatoid nodules, palpable purpura, vesiculobullous lesions, papules, ulcers and splinter hemorrhages. An accurate diagnosis is critical because many of the causes threaten life or limb, but the patient's medical history, accompanying non-dermatologic findings on physical examination and the use of discriminatory laboratory tests are usually more important than the nature of the cutaneous abnormalities [1]. The presence of blue toe syndrome requires the clinician to search for primary systemic vasculitides, as well as for malignancy, underlying infection, thrombosis, cardiovascular pathology and other diseases.

2. Case report

EA 53-year-old Caucasian male was admitted to the rheumatology clinic complaining of pain and violaceous discoloration of the toes, pitting edema of the left foot, a 15 kg weight loss over the previous month and tingling of the left lower limb. The skin changes of the toes preceded the other complaints by several months. The patient had no history of malignancy, infection, thrombosis, cardiac vegetations or coronary heart disease. The patient was not receiving any medications which could trigger thrombosis at the time of admittance.

2.1. Physical examination

Physical examination demonstrated pale skin and mucosae, violaceous discoloration of the toes with pitting

* *E-mail: marta_baleva@yahoo.com*

edema in the left foot (Figure 1) and a necrotic lesion of the second toe of the right foot. There were changes resembling clubbing on one of the fingernails. There were signs of mononeuritis multiplex in the left lower limb. The cardiac, pulmonary and neurologic examinations were unremarkable. The pulses were palpable in the peripheral arteries. The liver, spleen and peripheral lymph nodes were not enlarged.

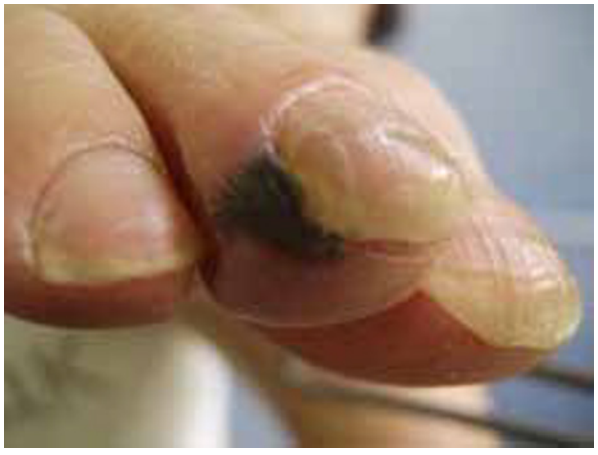

Figure 1. Necrotic lesion of the second toe of the right foot.

2.2 Laboratory data

Laboratory data demonstrated anemia, an elevated CRP and erythrocyte sedimentation rate, leukocytosis and thrombocytosis, increased serum creatinine and decreased creatinine clearance, increased gamma-glutamyl transferase and significant proteinuria. The immunological tests revealed elevated ANCA and anti-PR3 ANCA (c-ANCA) (Table 1).

The chest radiograph was normal, and hand films showed no changes of rheumatoid arthritis. Ultrasound of the abdomen revealed no tumor masses or abdominal lymph nodes. Doppler ultrasound of peripheral arteries revealed no abnormalities or stenoses. Echocardiography was normal.

The differential diagnosis was as follows: 1. primary vasculitis, including drug-induced vasculitis; 2. underlying malignancy; 3. underlying infection; 4. atheroemboli and cardiac vegetations; and 5. antiphospholipid syndrome. All the above diagnoses were consecutively ruled out due to the lack of specific clinical and laboratory findings that would support those conditions. The patient was therefore given a diagnosis of ANCA-associated vasculitis.

The patient was treated with methylprednisolone pulse therapy (1000 mg for 3 consecutive days), followed by methylprednisolone (1mg/kg body weight), in addition to pulse cyclophosphamide (1000 mg monthly) and heparin (30000 units / 24 h given by infusion pump). The decision to start corticosteroid therapy was due to its ubiquitous anti-inflammatory and immunosuppressive effect. The use of methylprednisolone in this patient was dictated particularly by its rapid and strongly predictable anti-inflammatory and immunosuppressive effect. The patient has so far been followed-up for 16 months and is currently clinically stable with a reduction of the blue toe area and a normal anti-PR3 ANCA. He will be followed-up for a total of 18 months.

Table 1. Laboratory data.

Laboratory Test	Patient Result	Normal Range
Hemoglobin	96 g/L	135 - 180 g/L
Erythrocytes	5 x 10^{12}/L	4.4 – 5. 9 x 10^{12}/L
CRP	156 mg/L	< 5 mg/L
ESR	80 mm/h	< 22 mm/h
WBC	15.2 x 10^{9}/L	3.5 - 10.5 x 10^{9}/
Platelets	442 x 10^{9}/L	130 – 360 x 10^{9}/
Creatinine	195 μmol/L	74 - 127 μmol/L
Creatinine clearance	25 ml/min	80 – 120 ml/min
AST	13 U/l	5 - 40 U/L
ALT	37 U/L	5 - 40 U/L
Alkaline phosphatase	64 U/L	56 - 119 U/L
GGT	154 U/L	5 - 50 U/L
CK	39 U/L	20 - 200 U/L
Glucose	5.42 mmol/L	2.8 – 6.1 mmol/L
Cholesterol	5.1 mmol/L	3.4 – 5.2 mmol/L
Proteinuria	5.5 g/24 h	< 0.150 g/24 h
Casts	10-20 erythrocytes, uric acid crystals, no bacteria or other cells	< 2 erythrocytes < 3 leucocytes
Urine microbiology	Negative	Negative
ANCA	1:1024	1:32
Anti-PR3	>100 U/ml	< 5 U/ml
Anti-MPO	1.2 U/ml	< 5 U/ml
ANA	negative	< 1:80
Cryoglobulins O.D.	negative	< 0.2
Rheumatoid factor	Negative	< 1:8
Anti-CCP	2 U/ml	< 5 U/ml
IgG ACL	4 GPL U/ml	< 22 GPL U/ml
IgM ACL	2 MPL U/ml	< 11 MPL U/ml
IgG B-2-GP I	4 U/ml	< 20 U/ml
IgM B-2-GP I	5 U/ml	< 10 U/ml
HBsAg	Negative	Negative
IgM HCV	Negative	Negative
Alpha fetoprotein	0 U/ml	0 – 6.7 U/ml
Carcino embryonic antigen	0 ng/ml	0 - 6 ng/ml
Prostate specific antigen	0 ng/ml	0 - 4 ng/ml
CA-19-9	0 U/ml	< 37 U/ml

3. Discussion

The cutaneous findings in primary and secondary vasculitides vary with the type and size of the vessels involved. Petechiae and purpura are the most common skin changes, but hives, an itchy papular rash, and painful or tender papules and nodules can occur. Other manifestations include ulcers and areas of necrotic skin, small black spots at the tips of the fingers or around the fingernails and toes (nail fold infarcts) or, more rarely, gangrene of the fingers or toes [2,3]. The blue toe syndrome can occur from vasculitis, malignancy, infection, thrombosis and other causes. In our patient, the blue toe syndrome was the initial manifestation of his ANCA-positive vasculitis, preceding other organ involvement by several months. The constellation of peripheral soft tissue edema, signs of mononeuritis multiplex, high grade proteinuria, high levels of c-ANCA, negative hepatitis markers, ANA and APL antibodies, and the lack of underlying malignancy, infection, embolism, thrombosis or cardiac vegetations, supported the diagnosis of ANCA-associated vasculitis.

4. Conclusion

Blue toe syndrome may be the first manifestation of different types of primary vasculitides.
The differential diagnosis comprises other autoimmune diseases, malignancy, underlying infection, thrombosis, cardiac vegetations etc. The presence of the blue toe syndrome should remind clinicians to search for systemic vasculitides, as well as for malignancy, underlying infection, thrombosis, emboli, cardiovascular pathology and other possible etiology.

Acknowledgments

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