Clinical Case Report

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Hypereosinophilic vasculitis

A case report

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Abstract

Introduction: The Revised International Chapel Hill Consensus Conference 2012 subdivides vasculitides based on combinations of features that separate different forms of vasculitis into definable categories. Hypereosinophilic vasculitis with sparing of the respiratory tract and renal system is a rare presentation that is yet to be described in the Revised International Chapel Hill Consensus Conference 2012 report that addresses nomenclature of vasculitides. This is a condition that involves a vascular injury due to either a primary eosinophilic vasculitis or an underlying connective tissue disease and it predisposes patients to a prothrombotic state.

Patient concerns: A 39-year-old patient presented with left hand digital ischemia, preceded by Raynaud phenomenon, and vasculitic rash. For 3 months, he was having digital ischemia affecting the left 2nd and 3rd digits in the form of pallor and gangrenous discoloration with a preceding history of a pinpoint pruritic rash affecting his lower limbs that extended to involve the trunk and upper limbs over a short period of time and responded to only a tapering dose of oral steroids. Examination revealed a delayed capillary refill in all left-hand digits and a weak left radial pulse but no bruit. The rest of his peripheral vascular examination was unremarkable.

Diagnosis: Investigations revealed an absolute eosinophilic count of 4.34 K/μL and erythrocyte sedimentation rate of 44 mm/h. A magnetic resonance angiogram showed a beaded appearance of the left ulnar artery distally and the radial artery branches in the left hand and subsequently was diagnosed with hypereosinophilic vasculitis.

Interventions: He was started on oral prednisone of 1 mg/kg daily orally tapering done as well as azathioprine for maintenance.

Outcomes: Two weeks postdischarge, the patient was seen in the outpatient department where his ischemic symptoms improved, and his skin rash healed. Noticed improvement in his splinter hemorrhages was also detected. He continued to do well on 2 years follow-up

Conclusion: This case reflects the importance of frequent reevaluation for vasculitic diseases criteria and nomenclature. Hypereosinophilic vasculitis with absent respiratory and renal involvement is a rare presentation with scarce evidence to guide treatment.

Abbreviations: ANA = antinuclear antibody, ANCAs = antineutrophil cytoplasmic antibodies, BUN = blood urea nitrogen, CHCC 2012 = Chapel Hill Consensus Conference 2012, EULAR = European league against rheumatism, HES = hypereosinophilic syndrome, IgE = immunoglobulin E, MRA = magnetic resonance angiography, PT = prothrombin time, PTT = partial thromboplastin time.

Keywords: antineutrophil cytoplasmic antibody-negative, hypereosinophilia, hypereosinophilic syndrome, hypereosinophilic vasculitis

1. Introduction

The Revised International Chapel Hill Consensus Conference 2012 (CHCC2012) subdivides vasculitides based on combinations of features that separate different forms of vasculitis into definable categories.[1] Our case is a presentation of a small to medium vessel antineutrophil cytoplasmic antibody (ANCA)-negative vasculitis with hypereosinophilia but no involvement of either the respiratory tract or the presence of glomerulonephritis. Having a negative ANCA vasculitis with eosinophilia is an uncommon presentation. This condition failed to be added to the pertinent consensus definition of vasculitides despite its importance and significance.

2. Case presentation

Our patient is a 39-year-old Arab male, a known case of dyslipidemia and a heavy smoker for 17 years, who was admitted to the hospital with 3 months history of digital ischemia affecting the left 2nd and 3rd digits in the form of pallor and gangrenous discoloration (with preceding history of Raynaud phenomenon) (Fig. 1). Upon questioning, he gave a history of a pinpoint pruritic rash affecting his lower limbs that extended to involve the trunk and upper limbs over a short period of time and responded to only a tapering dose of oral steroids. He also gave a history of typical angina chest pain for which he was previously admitted to

Editor: N/A.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2019) 98:17(e15392)

Received: 1 November 2018 / Received in final form: 25 March 2019 / Accepted: 2 April 2019

http://dx.doi.org/10.1097/MD.0000000000015392

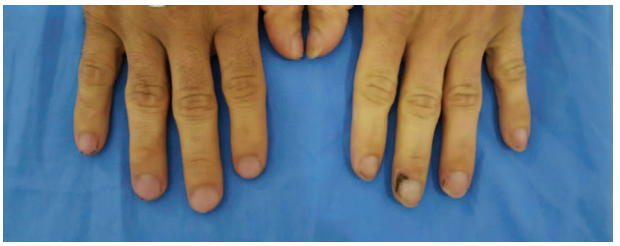

Figure 1. Ischemic changes in the form of unilateral pallor of the left hand in addition to multiple splinter hemorrhages and digital infarcts.

another hospital but was discharged on no antianginal measures after undergoing a coronary angiogram. No report of his workup was available. He had no history of any subjective fever, no oral or genital ulcers, and no respiratory symptoms. Also, there was no suggestive history of any autoimmune diseases in his family.

On physical examination, he was afebrile with normal blood pressure detected on both upper limbs with no limb difference. His hands showed a weak left radial pulse as compared to the right with no bruits detected on examination of left upper limb vasculature. His digits showed splinter hemorrhages and a distal infarction on the tip of his left ring finger (Fig. 2). There was reduced capillary filling detected in all digits of the left upper limb. The peripheral vascular examination was otherwise unremarkable. The lower limbs showed a vascular rash bilaterally below the knees (Fig. 3). A similar lesion was seen on the anterior abdominal wall. His systemic examination was otherwise noncontributory with normal neurologic, musculoskeletal, respiratory, ocular, cardiac, and abdominal examination.

Initial investigation showed white blood cell count of 12.4 K/μL (4–11) with absolute eosinophil count of 4.34 K/μL (4.7–6.1), hemoglobin of 13.9 g/dL (13–18), platelets of 253 K/μL (140–450), C-reactive protein 0.4 mg/dL (0–0.3), erythrocyte sedimentation rate 44 mm/h (0–20), blood urea nitrogen 23 mg/dL (7–18), creatinine 1.3 mg/dL (0.6–1.2), a total immunoglobulin E (IgE) level of more than 5000 (150–300), antinuclear antibody 1:320 that was homogeneous, 24-hour urine collection for proteins was 205 mg/24 hr (0–150), normal prothrombin time and partial thromboplastin time, normal electrolytes, and normal liver function tests with a normal abdominal ultrasound. Antibody screen was also done, and he only had an insignificant elevation of his anticardiolipin immunoglobulin G of 25.4 (≤14)

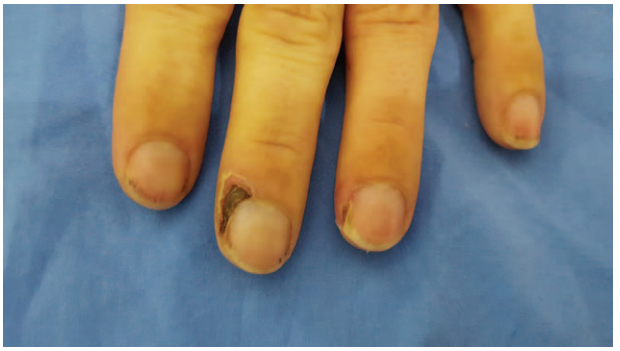

Figure 2. Splinter hemorrhage on the 2nd through the 5th left digits and distal ulceration on the tip of left 3rd and 4th digits.

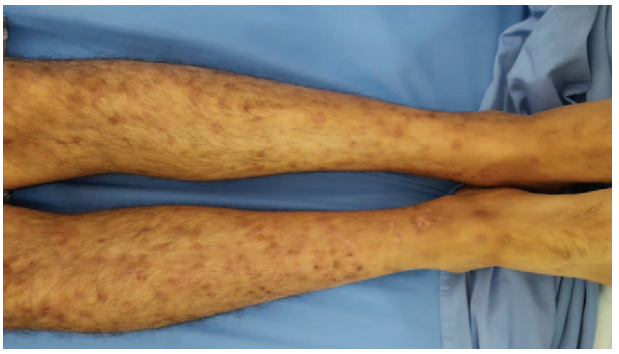

Figure 3. Scattered pinpoint healing vasculitic rash over the lower limbs.

and immunoglobulin M was 1.3 (0–1.2). Anti-B2 glycoprotein, ANCAs, myeloperoxidase antibodies, protease 3 antibodies, anti-double-stranded DNA, antiribonucleoprotein, anti-Sjogren antibody SSA and SSB, Smith antibodies, lupus anticoagulant, antiscleroderma antibodies (anticentromere antibodies and anti-Scl-70 antibodies), cryoglobulins, human immunodeficiency virus, and viral hepatitis profile were all negative. A transthoracic echocardiogram was also done and was normal with no evidence of vegetations, valvular involvement or wall motion abnormalities. A skin biopsy was sought but since there were no active skin lesions at the time of presentation, it would not be informative, although it was done in previous medical encounters and the results showed nonspecific dermatitis with lymphocytic and eosinophilia infiltration.

A magnetic resonance angiography (MRA) for his left upper limb was done and showed a beaded appearance of the left ulnar artery distally and the radial artery branches in the left hand suggestive of vasculitis yet there is evidence of good filling of the distal arteries (Fig. 4). The impression made was hypereosinophilic ANCA-negative medium and small vessel vasculitis for which treatment was started in the form of oral prednisone of 1 mg/kg daily orally as well as azathioprine.

Two weeks postdischarge, the patient was seen in the outpatient department where his ischemic symptoms improved, and his skin rash healed. Noticed improvement in his splinter hemorrhages was also detected. A plan is made to taper down his steroids gradually while maintaining him on Azathioprine. He continued to maintain his remission on 2 years of follow-up with no active lesions despite the presence of an eosinophil count of more than 1.5 K/μL during this period (Table 1).

3. Discussion

Vasculitic diseases are categorized depending on certain features that vary between different entities. They include the etiology, pathogenesis, type of vessel affected, type of inflammation, favored organ distribution, clinical manifestations, genetic predispositions, and distinctive demographic characteristics (Table 2).

Our patient had a unique presentation of Raynaud phenomenon (Fig. 5) with digital infarction of 2 digits, hypereosinophilia and high IgE level but no respiratory or renal involvement, and a vasculitic rash (Fig. 6). He also reported a consistent history of ischemic pattern chest pain that did not require the need for antianginal measures with no evident occlusion on coronary angiography. Angiography has been the gold standard for

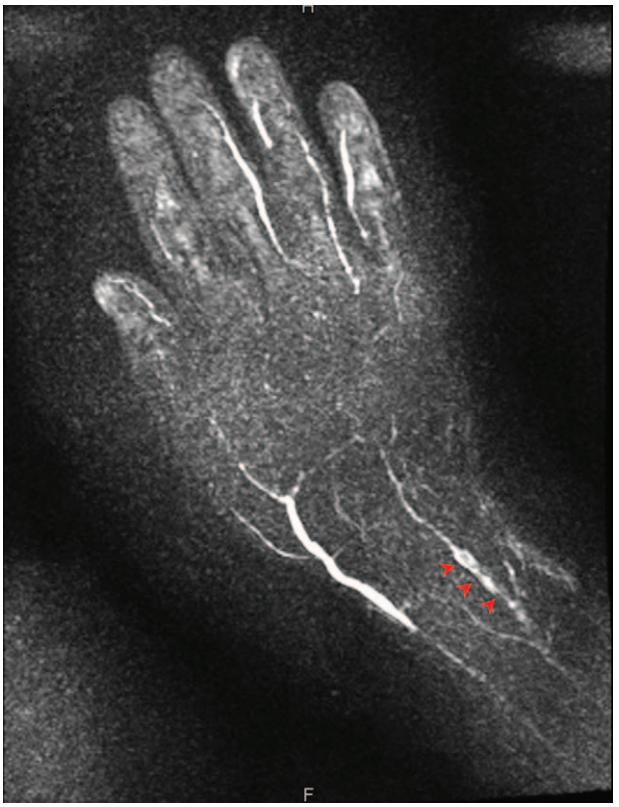

Figure 4. Beaded appearance of the left ulnar artery and the radial artery branches in the left hand on magnetic resonance angiography (MRA).

assessing medium- and large-vessel vasculitis for decades. More recently, the emerging of new less invasive imaging techniques with high sensitivity and specificity in assessing artery walls or inflammatory activity like MRA can often replace the use of angiography.[2,3]

Showing a beaded appearance of both ulnar and radial arteries that was found on MRA with proceeding history of Raynaud phenomenon points toward an involvement of middle to small vessel arteries. Although the presentation does not fit any criteria of the present vasculitic diseases mentioned in CHCC2012.[1] Thromboangiitis obliterans might be implicated but it is not supported by the previously mentioned imaging findings nor is associated with eosinophilia. Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome) is also a possibility but is far less likely with no pulmonary involvement along with a

Table 1

Patient eosinophil count during follow-up and inflammatory markers.

	1 month before presentation	At presentation	At 6 months	At 12 months	At 18 months
WBC	15.8	12.4	8.5	7.1	7.4
Eosinophils	42%	35%	25%	25%	22%
CRP, mg/dL	0.6	0.4	0.4	0.1	0.1
ESR, mm/h	59	44	25	22	15

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.

Table 2

Clinical manifestations of vasculitis based on vessel size affected.

Large*	Medium†	Small‡
Limb claudication	Subcutaneous nodules	Purpura
Asymmetric blood pressure	Ulcers (deep)	Infiltrated erythema
Absence of pulses	Livedo reticularis	Urticaria
Aortic dilation	Pitted palmar/digital scars	Vesiculobullous lesions
Bruits	Digital gangrene	Ulcers (superficial)
Constitutional symptoms§	Mononeuritis	Splinter hemorrhages
	Aneurysms	Scleritis, episcleritis, uveitis
	Infarct	Palisaded neutrophilic granulomatous dermatitis‖
	Erythematous nodules	Glomerulonephritis
	Hypertension (renal artery)	Gastric colic
	Constitutional symptoms§	Pulmonary hemorrhage
		Constitutional symptoms§

Adapted from Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. *American Journal of Clinical Dermatology* 2008 1;9(2):71–92.

* Large vessels (aorta and its branches) are not found in the skin. However, large-vessel vasculitic syndromes, giant cell arteritis, and Takayasu arteritis can rarely involve muscular arteries and small vessels of the skin.

† In the skin, medium vessels are the small arteries or small veins (diameter <800 μm, 4–8 medial muscular layers without distinct tunica adventitia) found in the subcutis or dermal-subcutis junction.

‡ Small vessels include arterioles, postcapillary venules, and capillaries found in both the dermis and subcutis.

§ Fever, weight loss, malaise, arthralgia, and arthritis are common to vasculitic syndromes of all vessel sizes.

‖ Also known as extravascular necrotizing granuloma. Small-vessel neutrophilic vasculitis is frequently seen in the vicinity of granulomas and necrosis.

negative immunologic screening. Secondary vasculitis predominantly occurs in relation to infections, drugs, and other rheumatic diseases, which it typically involves small vessels, but they were negative in this case. Having excluded viral causes of vasculitis along with what was mentioned before makes the most likely cause a different entity.[4,5] A major challenge in reaching an early definitive diagnosis in this case was the lack of an accessible biopsiable lesion.

Hypereosinophilic syndrome (HES) is a rare and underdiagnosed disorder, making it difficult to estimate overall prevalence. It is defined by the 3 criteria of having a persistent eosinophilia more than 1.5 K/μL for more than 6 months, lack of known causes of eosinophilia, and presumptive signs and symptoms of organ involvement (Fig. 7). Hypereosinophilic vasculitis is a condition that involves a vascular injury due to either a primary eosinophilic vasculitis or an underlying connective tissue disease. This predisposes patients to a prothrombotic state causing venous and arterial thrombosis.[6,7] All these elements were present in this case and the favorable response he had on treatment with reduction in the absolute eosinophilic count makes it the most likely diagnosis. This condition is still not yet included as a separate entity in the CHCC2012.

Vasculitides are chronic diseases that need lifelong treatment. This affects the short- and long-term management plans for these patients. Starting with steroids would give a quick resolution of the acute presentation and would be lifesaving as is evident by the literature and current practice. But the patients are in need to be bridged with another suitable immunosuppressant or modulator that ensure long-term remission of the disease and avoid long-term side effects of steroids. The British Society of Rheumatology in ANCA-associated vasculitis recommends the use of glucocorticoids and intravenous pulse cyclophosphamide or rituximab

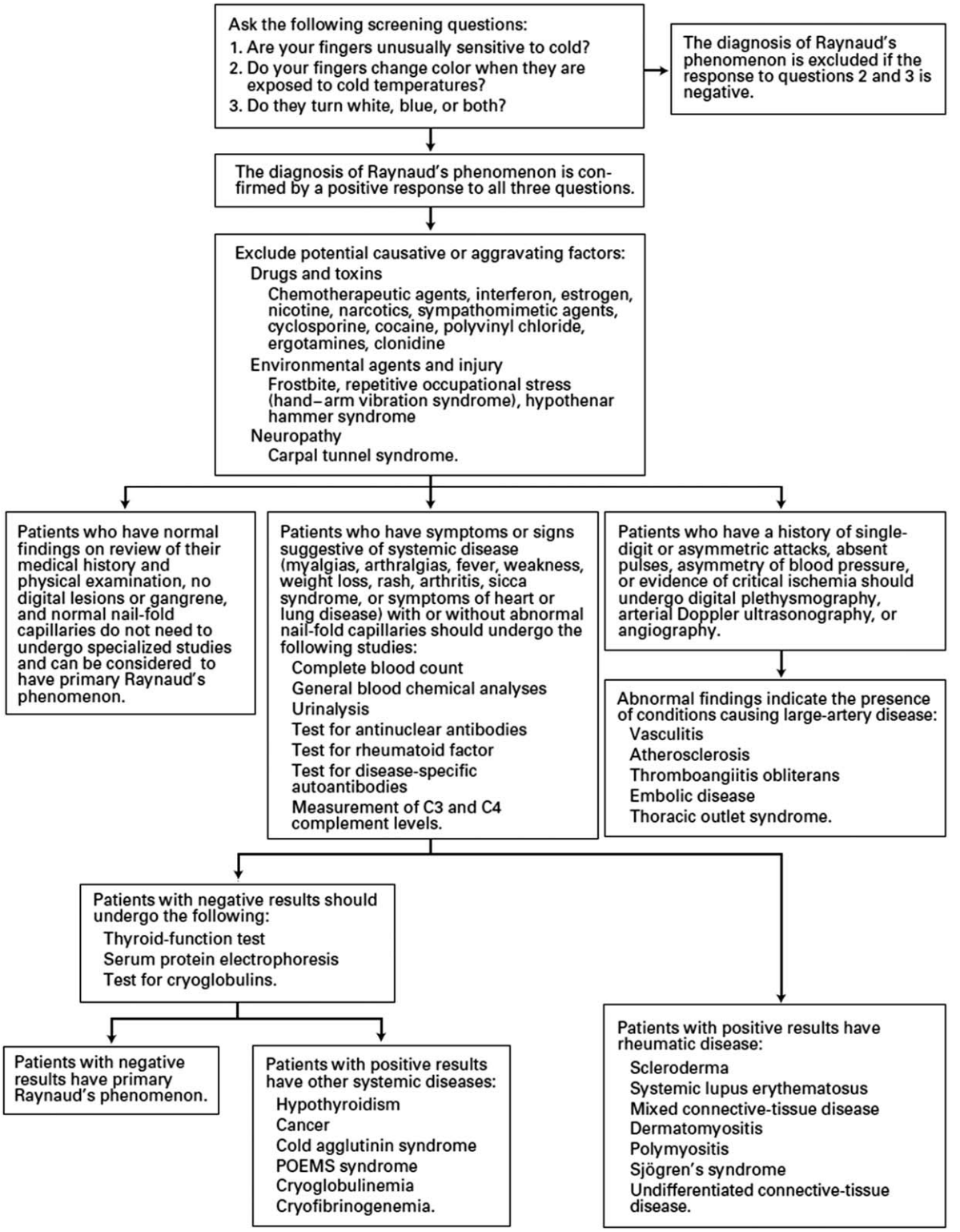

Figure 5. Approach to the diagnosis of Raynaud phenomenon adapted from Wigley FM. Raynaud phenomenon. *New England Journal of Medicine* 2002 26;347 (13):1001–8.

to establish disease remission and then maintain the clinical response with either azathioprine or methotrexate.[8] Mycophenolate mofetil or leflunomide may be used as alternatives for intolerance to or lack of efficacy of azathioprine or methotrexate. Rituximab may also be used as maintenance therapy. The European League against Rheumatism (EULAR) in collaboration with the European Renal Association and the European Vasculitis Society adds the consideration of plasma exchange

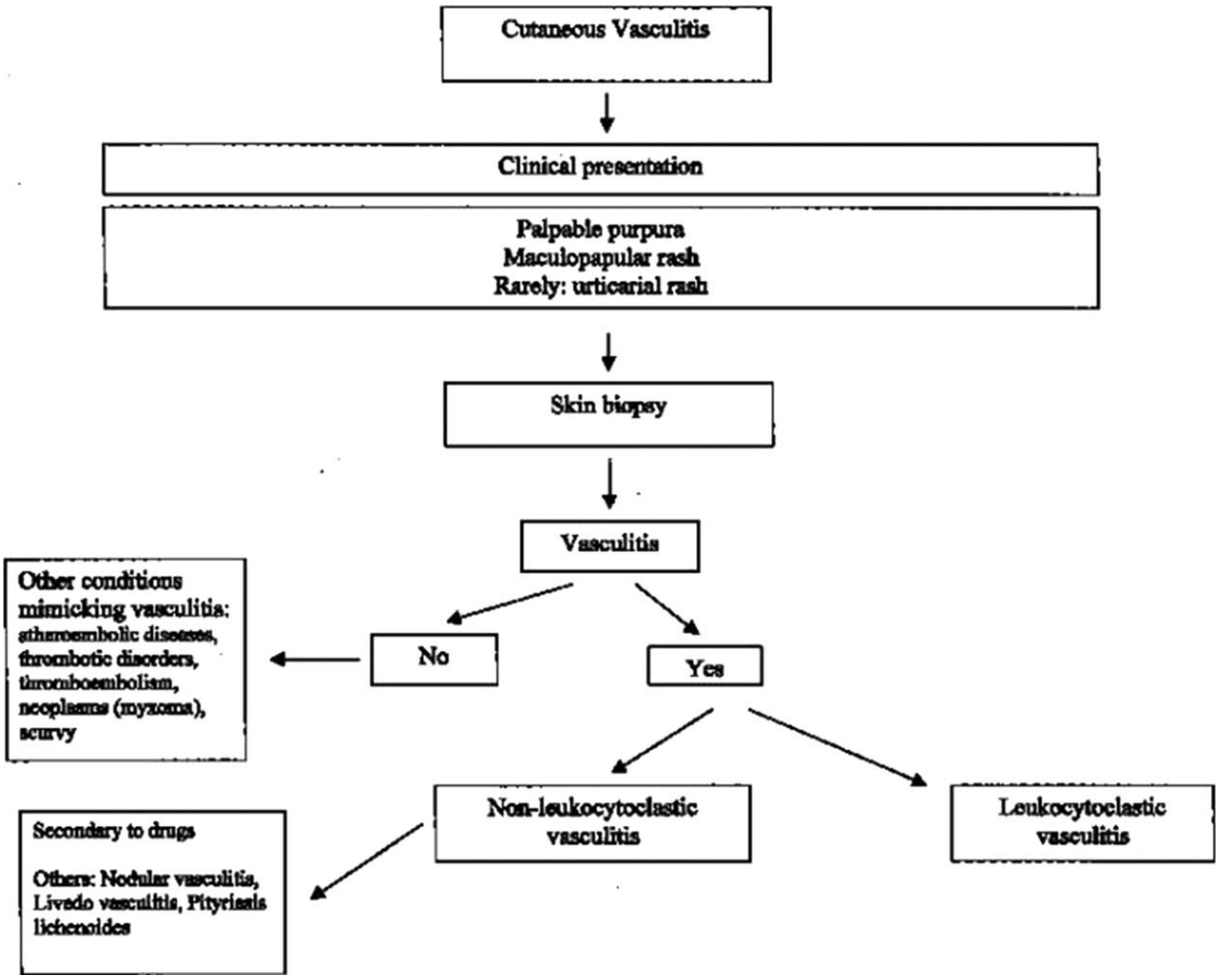

Figure 6. Diagnostic approach in a patient presenting with cutaneous vasculitis adapted Gonzalez-Gay MA, Garcia-Porrua C, Salvarani C, Scocco GL, Pujol RM. Cutaneous vasculitis: a diagnostic approach. *Clinical and Experimental Rheumatology* 2003 1;21(6; SUPP/32):S85–8.

in the presence of rapidly progressive renal failure or pulmonary hemorrhage in newly diagnosed ANCA-associated vasculitis.[9] These guidelines are mostly based on few randomized control trials, control trials without randomization, descriptive studies, and expert consensus. However, there is no mention of ANCA-negative vasculitis in these guidelines with clear lack of high quality evidence. The American College of Rheumatology has yet to release their vasculitis guidelines. In terms of treating HES per se, a high level of evidence is also still lacking and most of the recommendations are based on expert opinion (Table 3).

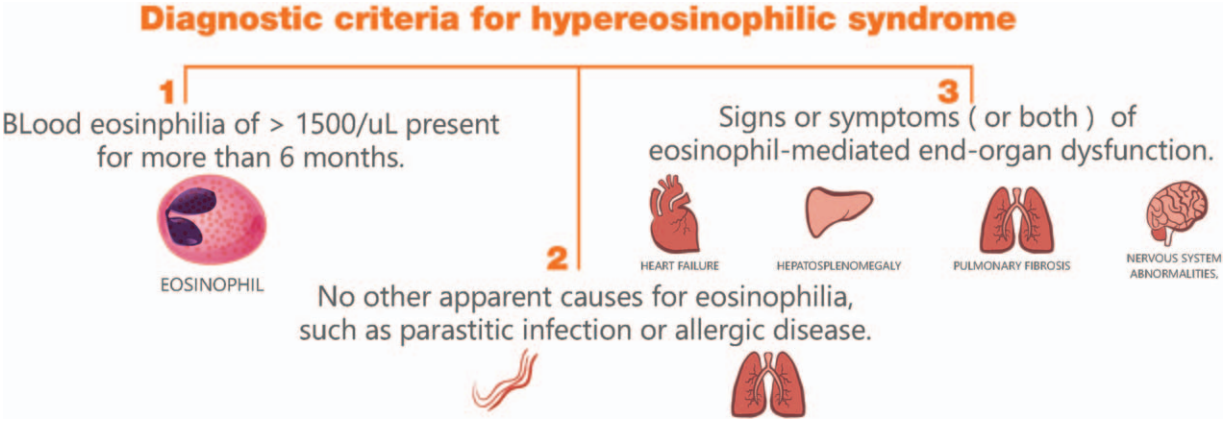

Figure 7. Diagnostic criteria for hypereosinophilic syndrome.

Table 3

Summary of treatment options for HES.

Treatment	Indications	Dose	Comments
Corticosteroids	First-line therapy unless FIP1L1/PDGFRA-positive	Varied	Initial dose 40 mg daily with slow taper to lowest effective dose
Hydroxyurea	Second-line therapy	1–3 g/d	Slow onset of action (1–2 wk)
Vincristine	Consider for counts >100,000/mm^3, including in children	1–2 mg intravenously	For rapid reduction of eosinophilia, not for chronic therapy
Other cytotoxic agents (including cyclophosphamide, 6-thioguanine, methotrexate, cytarabine, 2-CDA)	Consider for refractory HES unresponsive to corticosteroids, hydroxyurea, IFN-α	NA	Myeleran and 6-mercaptopurine have been consistently ineffective in published studies
IFN-α	Second-line therapy	1–2 mU sq daily	Slow onset of action (1–2 wk), pegylated IFN-α appears to have comparable efficacy
Anti-IL-5 antibody	Research indication to date	≤750 mg/kg monthly	Currently unavailable except in clinical trials or for compassionate use (mepolizumab; GlaxoSmithKline)
Other immunomodulatory therapy (including alemtuzumab, cyclosporine, IVIG)	Consider for refractory disease	NA	Little published data
Imatinib mesylate	First-line therapy for FIP1L1/PDGFRA positive and myeloproliferative variant, consider for other refractory disease	100–400 mg daily	With corticosteroids if cardiac involvement, not useful in lymphocytic variant
Bone marrow transplant	FIP1L1/PDGFRA positive and imatinib resistant FIP1L1/PDGFRA-negative with disease progression despite conventional therapies	NA	Nonmyeloablative

Adapted from Klion AD, Bochner BS, Gleich GJ, Nutman TB, Rothenberg ME, Simon HU, Wechsler ME, Weller PF, Hypereosinophilic Syndromes Working Group. Approaches to the treatment of hypereosinophilic syndromes: a workshop summary report. *Journal of Allergy and Clinical Immunology* 2006 30;117(6):1292–302.

CDA = chlorodeoxyadenosine, FIP1L1 = Fip1-like 1, HES = hypereosinophilic syndrome, IFN = interferon, IVIG = intravenous immunoglobulin, NA = not applicable, PDGFRA = platelet-derived growth factor receptor α.

Furthermore, it is noteworthy that monitoring peripheral blood eosinophilia is a reasonable approach in following these patients but in fact there is no clear relation between organ damage and eosinophilic count.[10] Thus, the clinical response and patient symptoms are the main drive in decision making until the development of more specific and accurate disease activity markers and in this case the absolute eosinophilic count was still elevated but trending down which was reassuring.

4. Conclusion

Even with the advances since the proposed nomenclature of the CHCC2012, there are still yet some entities of vasculitis that need to be defined. Frequent reevaluation for vasculitic diseases criteria appears to be essential. ANCA-negative vasculitis with hypereosinophilia in the setting of absent respiratory and renal involvement is an uncommon presentation. MRA has a corner stone place as a noninvasive imaging technique that can replace angiography and improve diagnosis in the absence of an accessible biopsy.

Author contributions

- Dr Husam Alzayer: constructed the idea of the case, reviewed the literature, and designed the manuscript
- Dr Manal Hasan: constructed the idea of the case and revised the manuscript critically for important intellectual content and approved it for publication

Supervision: Manal Ahmed Hasan.
Writing – original draft: Husam Alzayer.
Writing – review & editing: Husam Alzayer, Manal Ahmed Hasan.

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