CASE REPORT

Unravelling the NERDS syndrome

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SUMMARY

A 22-year-old man presented with symmetric polyarthritis, pruritus and deviation of angle of mouth to the right side since the last 7 years. His symptoms were persistent despite receiving ayurvedic medications and symptomatic therapy. Examination revealed dry skin, cutaneous nodules, xanthelasma, periarticular non-tender swellings, pitting oedema of hands and feet and lower motor neuron type right facial palsy. Haematological investigations revealed eosinophilia and skin biopsy had cutaneous eosinophilic infiltration. The constellation of above findings comprises the nodules, eosinophilia, rheumatism, dermatitis and swelling syndrome. It a rare syndrome with few reported cases in literature. The patient was started on oral corticosteroids which was subsequently tapered and methotrexate therapy. His polyarthritis and skin rashes resolved with therapy. He has been followed-up for 2 years and is presently asymptomatic for the last 1 year.

BACKGROUND

The nodules, eosinophilia, rheumatism, dermatitis and swelling (NERDS) syndrome is an enigmatic, rarely diagnosed entity with distinct clinical manifestations. The lack of knowledge about the condition is a major hindrance to its early recognition and subsequent management. Our case would enrich the current knowledge of this condition and help in sensitising physicians for diagnosing similar illnesses. The therapy outcomes and observations from follow-up will further guide evidence-based management of such illnesses in the future.

CASE PRESENTATION

A 22-year-old man from rural India presented with a history of bilaterally symmetrical polyarthritis involving small and large joints of upper and lower limbs, including the distal interphalangeal joints, since the age of 5 years. He had associated intermittent, generalised itching predominantly affecting the palms and soles. He developed acute onset deviation of the mouth to the right side first noticed at

the age of 15 years which was acute in onset and non-progressive in nature. There was no history of fever, atopy, Raynaud's phenomenon, photosensitivity, eye symptoms or proximal weakness. There was no history suggestive of hypothyroidism, sicca symptoms, mental retardation or developmental delay, and the family history was not significant. He was diagnosed as a case of juvenile idiopathic arthritis and had received ayurvedic medicines for his complaints without any symptomatic relief. For the above complaints, he was referred to our centre for further evaluation and management.

At admission, his vitals were stable. On examination, he was found to have xanthelasma and dry skin with dermatographism ([figure 1](#)). There were periarticular, non-tender soft tissue swelling around the wrist, metacarpophalangeal, proximal and distal interphalangeal joints. He also had bilateral pitting pedal oedema and left-sided lower motor neuron facial palsy ([figure 1](#)). He had firm cutaneous nodules over the elbows, wrists, scrotum, legs, distal and proximal interphalangeal joints ([figure 2](#)).

INVESTIGATIONS

Blood investigations ([table 1](#)) revealed leucocytosis with predominant eosinophilia (total leucocyte count, 26 560/ μ L; absolute eosinophil count, 19 840/ μ L). Eosinophilia workup was unremarkable ([table 2](#)). Serum IgE level was found to be raised (4273 IU/mL, normal range 1.5 to 378 IU/mL). Inflammatory markers revealed an abnormally high C reactive protein level (10.6 mg/L) with a normal erythrocyte sedimentation rate. Serum ACE level was 22 IU/L (normal range <40 IU/L). On immunological testing, antinuclear antibody, antineutrophil cytoplasmic antibody, antiproteinase and antityeloperoxidase antibodies and rheumatoid factor and anticyclic citrullinated peptide antibodies were found to be negative. Metabolic parameters and lipid profile were within normal range. Urinalysis and stool microscopy did not yield any abnormality. Ophthalmological examination and pulmonary function tests were also within normal limits.

Figure 1 Showing characteristics of the patient on physical examination: (A) dermatographism; (B) dermatitis; (C) left sided facial palsy.

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Figure 2 Showing nodular swellings (black arrows) at (A) proximal interphalangeal joint; (B) elbow and (C) wrist joint.

Chest X-ray, ultrasound of the abdomen and echocardiography were normal. Bone scan was suggestive of polyarthritis involving bilateral wrists, small joints of both hands, bilateral knee joints, bilateral ankle joints and bilateral sacroiliac joints.

Bone marrow examination revealed 83% eosinophils with mature forms and a myeloid-to-erythroid ratio of 1:1, but no blasts on aspirate and a normal cellularity with predominant eosinophils and their precursors on bone marrow biopsy. Skin biopsies performed from eyelid and elbow are elucidated in figure 3. It revealed capillary proliferation with chronic inflammatory cells with excess of eosinophils.

DIFFERENTIAL DIAGNOSIS

Since the patient presented with polyarthritis with cutaneous nodules, pitting pedal oedema with facial palsy along with hyper-eosinophilia, hypereosinophilic syndrome (HES) was kept as our differential diagnosis. We also considered Well's syndrome, eosinophilic vasculitis and Gleich syndrome (table 3). However, most of the manifestations can be seen in a rare clinical entity called NERDS syndrome.

TREATMENT

There have been only three reported cases of NERDS syndrome in literature and thus there are no standard treatment protocols for its management. He was started on prednisolone tablet (40 mg/ day), which was gradually tapered (5 mg every 2 weeks). The patient had relapse of arthritis on tapering dosage (15 mg/ day) of prednisolone when methotrexate (15 mg/week) along with folic acid (5 mg/week) was added. Prednisolone was stopped

Table 1 Showing haematological investigations done for the patient

	Initial visit	Three weeks after therapy
Haemoglobin (gm/dL)	10.7	12.2
Total leucocyte count (cells $\times 10^9/L$)	26.560	10.300
DLC (%)	N 19, E 71	N 52, E 32
Platelet count (cells $\times 10^9/L$)	250	320
Absolute Eosinophil count (cells $\times 10^9/L$)	19.840	3.296
CRP (mg/dL)	10.6	6.2
ESR (mm/hour)	07	08
LFT/RFT/lipid profile/RBS	WNL	WNL
Serum uric acid (mg/dL)	4.5	5.3
CPK/LDH	WNL	—

AEC, absolute eosinophil count; CPK, creatinine phosphokinase; DLC, differential leucocyte count; LDH, lactate dehydrogenase; LFT, liver function test; RBS, random blood sugar; RFT, renal function test; WNL, within the normal laboratory limits.

Table 2 Showing eosinophilia work-up done for the patient

Urine routine exam	Normal
Serum IgE levels (IU/L)	4237.2 (15–378)
Stool ova cyst, occult blood	Negative
Peripheral smear for microfilarial parasite	Negative
ECG/Chest X-ray	Normal
Ultrasound of the abdomen	Normal
TTE	Normal

TTE, transthoracic echocardiogram.

after 3 months of initiating methotrexate but he continues to take Methotrexate 15 mg/ week.

OUTCOME AND FOLLOW-UP

There was resolution in the swelling, arthritis and eosinophilia after about 2 week of therapy. There was no response in his facial palsy, nodules and finger deformitis. He is on regular follow-up since the last 2 years and is symptom free at present. There are no new nodules or progression of the finger deformities or his facial palsy.

DISCUSSION

Our patient presented with childhood onset polyarthritis with associated pruritic skin rashes, cutaneous nodules and developed facial nerve palsy few years later. Additionally, he had evidence of dermatitis, dermographism, periarticular swellings along with peripheral and tissue eosinophilia. Though eosinophilia can be a component of certain connective tissue disorders, the constellation of rheumatism, allergic skin changes, and primary eosinophilia can be attributed to the 'hypereosinophilic syndrome (HES)'.

The diagnostic criteria for HES were first described by Chusid in 1975.¹ The presence of persistent eosinophilia $>1500/mm^3$ for more than 6 months with lack of any other secondary causes for eosinophilia was a prerequisite for the diagnosis of HES. These along with manifestations of end-organ damage secondary to eosinophilia including skin, heart, nervous system and so on would qualify as HES. In 2010, to address the improved understanding of the disease and to circumvent the lacunae of the previous criteria, the definition of HES was suitably modified.² The time limit of 6 months has been eliminated. Patients with eosinophilia ($>1500\text{cells}/\text{mm}^3$) on two separate occasions or marked tissue

Figure 3 Skin biopsy from eyelid showed epidermal inclusion cyst with foreign body giant cell reaction: (A) cyst in the dermis; (B) keratin flakes (Starr) with histiocytic and multinucleated giant cells (arrow). Skin biopsy from elbow showed (C) mild irregular acanthotic epidermis; (D) capillary proliferation (arrow) extending in to the subcutaneous tissue; (E) chronic inflammatory cells with excess of eosinophils; (F) eosinophilic cells in higher power.

Table 3 Differential diagnosis considered for the patient

Arthritis with nodules	
Rheumatoid arthritis	Rheumatoid factor always present. Common on pressure points like olecranon.
Drugs (MTX, anti-TNF, AZA)	MTX may lead to accelerated nodulosis in some patients of RA. May necessitate discontinuation of therapy.
Gout	Lesch-Nyhan syndrome (juvenile gout): X-linked recessive condition due to HGPRT deficiency, onset first year of life, hyperuricaemia, self-mutilation like lip and finger biting, psychiatric symptoms, poor muscle control, movement disorder, cognition problems, megaloblastic anaemia
Prurigo nodularis	Pruritic nodules usually on arms or legs. Commonly presents with multiple excoriated lesions caused by scratching.
Angiolymphoid hyperplasia	Persistent subcutaneous nodules on the head and neck with distinctive histological features of angiolymphoid hyperplasia with eosinophilia without systemic manifestations.
Arthritis with eosinophilia	
Eosinophilic arthritis	Acute arthritis of large joints with urticarial rash, with eosinophilia, without systemic involvement, complete resolution of symptoms with NSAIDs/steroid/Diethylcarbamazine
Hypereosinophilic syndrome	<ol style="list-style-type: none"> 1. Blood eosinophilia $>1500/\text{mm}^3$ on at least two occasions or evidence of prominent tissue eosinophilia-associated with symptoms and marked blood eosinophilia 2. Exclusion of secondary causes of eosinophilia 3. Organ dysfunction/systemic involvement with evidence of eosinophilic infiltration
Rheumatoid arthritis	Eosinophilia can be an extra-articular manifestation
Drugs	MTX, Sulfasalazine
Predominantly skin restricted eosinophilic disorder	
Gleich's syndrome	Recurrent episodic of angioedema, urticaria, fever, high-serum IgE levels with eosinophilia. No other system involvement
Well's syndrome	Urticarial lesions with bacterial cellulitis like skin lesions—chronic recurrent eosinophilic cellulitis, rarely facial nerve palsy, arthralgia, myalgia with eosinophilia
Hypereosinophilic dermatitis (pachydermatous eosinophilic dermatitis)	Generalised polymorphous skin eruptions, hypertrophic genital lesion, eosinophilic rich lymphohistiocytic cutaneous infiltrate, elevated LDH, eosinophilia
NERDS	Rare hypereosinophilic disorder with poorly understood long-term prognosis

Anti-TNF, antitumour necrosis factor; AZA, azathioprine; LDH, lactate dehydrogenase; MIARN, methotrexate-induced accelerated rheumatoid nodulosis; MTX, methotrexate; NERDS, nodules, eosinophilia, rheumatism, dermatitis and swelling; RA, rheumatoid arthritis.

eosinophilic infiltration with AEC <1500 cells/ mm^3 can be diagnosed as HES. End-organ damage is no longer considered a prerequisite for diagnosis as a subgroup of patients may never develop organ damage (hypereosinophilia of undetermined significance). The persistent eosinophilia in our patient along with the absence of secondary causes for the same fulfils the criteria for HES.

Arthralgias, non-erosive arthritis, large joint effusions with synovial fluid eosinophils can be found in HES.³ The non-erosive joint involvement in our patient along with resolution of symptoms with corticosteroid-based therapy provides further credence to these findings. Skin is one of the most frequently involved organs in HES.⁴ A study by Ogbagu *et al* found 69% of the patients to have cutaneous manifestations of which dermatitis and pruritus were the most common manifestations⁵ followed by angioedema, urticaria and cellulitis (Well's syndrome).

Well's syndrome is a rare eosinophilic dermatosis characterised by recurrent annular, pruritic and painful skin lesions. It is strongly related to hypereosinophilia.⁶ Though it can be associated with arthralgias, the absence of painful lesions in our patient with lesions which were morphologically distinct from Well's syndrome makes it an unlikely diagnosis. Eosinophilic vasculitis (cutaneous necrotising vasculitis)⁷ is characterised by eosinophilic infiltration of the vessel wall. It can be associated with HES where it presents with erythematous, pruritic or purpuric skin lesions with peripheral blood eosinophilia. The presence of vasculitis leading to mononeuritis can also explain for the left-sided facial nerve palsy seen in our patient. However, the childhood onset arthritis and absence of fibrinoid necrosis on skin biopsy do not support such a diagnosis. The Gleich syndrome is characterised by recurrent angioedema, urticaria and marked hypereosinophilia.⁸ However, the absence of periodicity in our case and other peculiar features of this syndrome rules it out.

The prominent nodules and periarticular swelling in our patient can be a component of the underlying joint inflammation.

However, this has infrequently been described with HES. The perplexing constellation of manifestations seen in our case can be seen in a rare clinical syndrome called NERDS syndrome, which was first described by Butterfield *et al*.⁹ As of this day, there have been only three such cases described in the medical literature. The index case as described by Butterfield *et al* was a 20-year-old woman who had nodules, episcleritis and recurrent urticaria along with eosinophilia. Nodule biopsy revealed necrotising granulomas with non-specific vasculitis. She was treated with the alternate day, low-dose oral corticosteroid therapy. She was followed-up for 15 years and showed a good response to therapy. The second case⁹ presented at an age of 27 years with pruritic dermatitis, non-limiting arthralgias with skin nodules. Both the patients had eosinophilia, elevated serum IgE levels and tissue eosinophilic infiltration. The third case as described by Zenarola *et al* presented with rheumatism, xerosis and periarticular nodules.¹⁰ There was associated tissue and blood eosinophilia. These cases provide further credence to the diagnosis of our patient.

As the evidence regarding management of NERDS syndrome is limited, the literature regarding HES management was used to guide therapy. Systemic corticosteroid therapy is the mainstay of HES therapy. In a multicentre study, 85% of the 188 HES patients achieved partial or complete remission within 1 month of therapy.⁵ The favourable treatment achieved in our case further attests these findings. Considering the long-term side-effects of corticosteroid therapy, initiation of steroid-sparing agents like methotrexate, azathioprine is usually necessary following remission. The other treatment options include hydroxyurea, interferon alpha and omalizumab,⁴ but the efficacy and safety results of these drugs are not sufficient to use them as first-line therapy.

Our case highlights the role of HES in evaluating rheumatological ailments. Though facial nerve paresis along with NERDS or HES has not been described in the literature, the possibility of underlying eosinophilic vasculitis cannot be ruled out. The

Patient's perspective

- ▶ I have been in pain for the most part of my life. Initially it was dismissed as likely due to some trivial injury, later thought of as an excuse not to study. When the swellings appeared throughout the body, and I was covered in rashes only then did my disease get its due attention first from my parents and then from the doctors. Though the initial medications brought some temporary relief but the frequent relapses of pain and requirement of continuous medications led us from one doctor to another. We also took advice from all the priests and holy men in town. Ayurvedic medications brought about some relief but a complete cure was still a dream. Despite the various measures my pain and swelling persisted.
- ▶ When I was informed that I have 'Childhood joint problem of adult people' I was not sure what to expect from the disease. Initially there was some response with the medications but it led to severe abdominal pain and I discontinued the medications. It was wrong of me in retrospect and I would never do such a mistake again. Just as I had learned to live with my pain, one day I was told I looked funny. I could not believe my doctor when he said that I have suffered from likely paralysis of my face. I was told there is a possibility of spontaneous recovery and nothing much can be done anyway. The advised tests were costly and due to financial constraints we did not pursue further treatment.
- ▶ The problems of my health never ceased and it was gradually increasing. With unbearable itching and joint aches, I came to New Delhi hoping for a miracle. Wherever I went, doctors used to surround me and keep discussing among themselves of the various possibilities I could have had. I was more like a research topic than a patient for them. After 1 month of hospitalisation and countless needle pricks when I was told about my new disease, I did not understand it. I still don't. All I wanted to know then and now is whether there is a permanent cure. How can I get rid of this disease and become like everyone else?
- ▶ The treatment brought significant improvement in my condition. The second week of therapy was the first pain-free period of my life. Finally, I am able to resume my normal life, get a job and earn myself a decent living. I am happy with my current state of health but I do wish that one day there would be an absolute cure for this condition and I will not have to take any medications.
- ▶ I understand that my condition is an uncommon one, and this is the reason it was so frequently missed. I wonder had my first doctor told me about this disease, my life would have been so much different. I could have completed my formal education, would have had earned more and could have supported my family better. I wish nobody has to suffer from such a disease. If anybody does, hopefully he would be diagnosed and treated early. Thank you for letting me express my aspect of this disease.

Learning points

- ▶ Hypereosinophilic syndrome (HES) can present with various manifestations and is an important differential of conditions with raised serum eosinophils.
- ▶ HES definition has undergone considerable changes; duration of the disease and the presence of organ damage are no longer essential for the diagnosis.
- ▶ Nodulosis, eosinophilia, rheumatism, dermatitis and swelling syndrome is a rare type of hypereosinophilic disorder.
- ▶ The syndrome presents with good response to corticosteroid-based therapy.
- ▶ Other differentials like the Well's syndrome and Gleich syndrome must be considered while evaluating such cases of HES with skin changes.

successful management of this rare syndrome further equips us with knowledge to efficiently and promptly manage such cases in the future. The full spectrum of manifestations, disease course and treatment options of NERDS syndrome requires further research.

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