CASE REPORT

Hypereosinophilia and severe bone disease in an African child: an unexpected diagnosis

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SUMMARY

Hypereosinophilic syndromes are rare in children. Sporadic, mild-severity FIP1L1-platelet-derived growth factor receptor α (PDGFRα) rearrangement cases have been reported, mainly in boys. We present the case of a 5-year-old girl referred from her African country of birth, due to severe constitutional symptoms, multifocal bone pain, headache, gastrointestinal complaints, cardiomyopathy and unexplained hypereosinophilia. She presented multiple end-organ diseases and striking bone involvement. Although she had a positive serology for *Strongyloides stercoralis*, extensive evaluation detected a FIP1L1-PDGFRA fusion gene. Systemic corticosteroids and low-dose imatinib were started and the child became asymptomatic. After 9 months of treatment, FIP1L1-PDGFRA was no longer detected.

BACKGROUND

Hypereosinophilic syndrome (HES) is characterised by chronic eosinophilia (above 1500×10^9/L) with end-organ involvement and is uncommon in children.[1 2] FIP1L1-platelet-derived growth factor receptor α (PDGFRα) (FP) rearrangement is the most frequently identified clonal event.[1] This distinct group of haematopoietic disorders is highly sensitive to low-dose imatinib mesylate treatment.[3 4] However, because of its exceptional occurrence in this age group, a high index of suspicion is needed to establish the diagnosis.[3]

CASE PRESENTATION

A previously healthy 5-year-old girl was referred to our institution from her native country of Cape Verde for severe eosinophilia evaluation that had not improved after several antibiotics, albendazole and mebendazole.

She presented with a 1-year history of malaise, fatigue, anorexia, weight loss (−25% of her body weight in 6 months), recurrent fever, vomiting, occasional bloody diarrhoea, headache and intense right leg pain that progressed to multifocal involvement (right hip, knee and ankle, and fingers). She denied asthma.

On admission, she appeared ill and emaciated (body mass index (BMI) z-score −2.99), with pale mucosae, numerous infracentimetric supraclavicular and axillary lymph nodes, a grade II systolic murmur, hepatosplenomegaly and diffuse swelling of the second and third right-hand fingers.

INVESTIGATIONS

Initial evaluation revealed leukocytosis with significant hypereosinophilia (white blood cells (WBC) 59.790×10^9/L: neutrophils 16.770×10^9/L, eosinophils 29.430×10^9/L, lymphocytes 6.360×10^9/L, monocytes 3.910×10^9/L and basophils 320×10^9/L); mild normocytic anaemia (8.3 g/dL); normal platelet count; anisopoikilocytosis, teardrop cells and ovalocytes; CRP 22 mg/L; erythrocyte sedimentation rate 53 mm/hour; ferritin 536 ng/mL; IgE 232 kUI/L; hypergammaglobulinaemia 20.3 g/L; high LDH; serum B12 above 2000 pg/dL and normal serum tryptase.

Prompt evaluation for aetiology and possible end-organ involvement were undertaken.

A transthoracic echocardiogram revealed mitral valve regurgitation and thickening, and enlargement of both left atrium and ventricle; troponin I, CK-MB and brain natriuretic peptide were normal; carvedilol was initiated. Abdominal ultrasound and computed tomography examinations showed hepatosplenomegaly, gallbladder wall thickening and several mesenteric and axillary lymphadenopathies; alanine transaminase (ALT), aspartate transaminase (AST) and AP were within normal range. Cranial magnetic resonance imaging with additional magnetic resonance angiography showed multifocal white matter lesions with mild T2/FLAIR enhancement and no vascular pathologic lesions. Cerebrospinal fluid analysis was normal.

Radiological skeletal survey revealed a poorly defined sclerotic and lytic involvement of the axial and appendicular skeleton, more pronounced in the femurs (figure 1A) and pelvis (figure 1B), with areas resembling myelosclerosis. Spiculated irregular periosteal reaction was seen on the iliac bones (figure 1C).

Extensive study for infectious causes detected positive *Strongyloides stercoralis* serum IgG (EIA), without larvae on stool culture. The patient received albendazole and a 7-day course of ivermectin. Other infectious diseases (*Toxocara*, *Leishmania*, *Entamoeba histolytica*, *Cysticercus*, cytomegalovirus, epstein-barr virus, human immunodeficiency virus, hepatitis C virus, hepatitis B virus, hepatitis A virus, Parvovirus, *Bartonella henselae* and *Mycobacterium tuberculosis*) were excluded.

Bone marrow was hypercellular, mainly of the myeloid lineage, with numerous eosinophils (20%–30%) and showed severe myelofibrosis without dysplastic changes, blasts or increased mastocytes. Immunohistochemistry for the expression of CD34, HLA-DR, CD117 and CD1a was negative.

FP fusion gene was detected by RT-PCR and fluorescent in situ hybridization (4q12 deletion/CHIC2 in 56% of 117 nuclei).

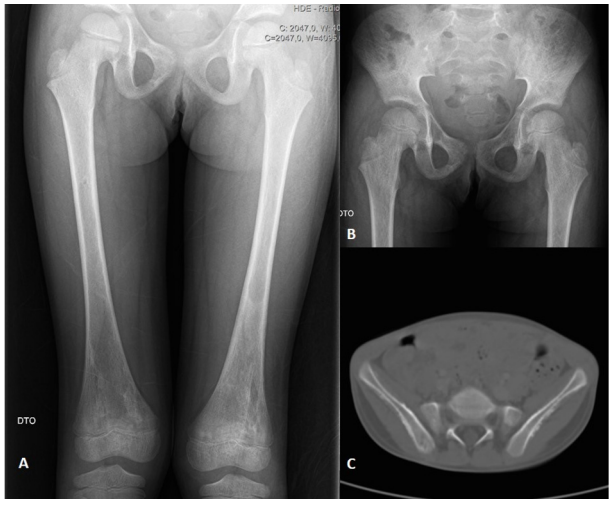

Figure 1 (A) AP radiograph shows poorly defined mixed sclerotic and lytic distal metadiaphyseal areas with relative epiphysial sclerosis. No periosteal reaction is seen. (B) Diffuse sclerosis of the pelvic bones with no cortical disruption and no associated arthropathy. No focal lesions are seen. (C) Pelvic CT showed diffuse spiculated periosteal reaction along the iliac bones with cortical sclerosis and some poorly defined lytic medullary areas.

TREATMENT

On the third day of ivermectin, the patient started imatinib (100 mg/day, ~133 mg/m^2/day) and concomitant methylprednisolone (1 mg/kg/day for 14 days). Within 3 days, clinical improvement (including bone pain resolution) and eosinophil count normalisation was observed, followed by complete remission of all signs and symptoms.

Imatinib was suspended three times for a 2-week period, each time due to asymptomatic transient increased liver enzymes (maximum AST 813 U/L [24 × upper normal limit] and ALT 1035 U/L [18 × upper normal limit]), non-responsive to dosage reduction. Nevertheless, after 9 months of treatment, RT-PCR for FP rearrangement became persistently negative, and imatinib was tapered down to 54 mg/m^2/day (100 mg on alternate days). WBC and eosinophil count remained normal throughout the treatment.

OUTCOME AND FOLLOW-UP

Currently, 16 months after FP negativity, she's still on low-dose imatinib, remains asymptomatic and in molecular remission. On echocardiogram follow-up, dilated cardiomyopathy has resolved.

DISCUSSION

Evaluation and treatment of paediatric patients with HE is challenging. HES are rare in children and the cause is often undetermined.[3] Indeed, in Rapanotti *et al*[5] review of 10 children with HES, only one presented the FP gene fusion and so far only a few cases have been published.[6–10]

A significant male predominance is observed in children with HES[10] and clinical presentation is highly variable although usually mild.[6] Here, we report an extremely severe presentation of HES with FP rearrangement in a female child, to the best of our knowledge the most severe one, with multiorgan involvement (including probable cardiac, gastrointestinal and central nervous system affectation; although, without histopathological examination, this cannot be fully confirmed).

Aside from prominent general symptoms, our patient also presented distinctive features, such as arthritis[8] and bone pain, only sporadically described in HES.[11 12] She had an apparently worse course than the previously described FP-child with bone pain,[7] developing multiple focal lesions. In addition, unique striking bone lesions, trabecular infiltration and secondary myelofibrosis, which was rarely described in relation to HES,[13 14] were observed in this case, possibly related to the prolonged disease course.

We are acquainted that, in African migrants, *Strongyloides* is still the most common identified cause of eosinophilia. Indeed, EIA serology is highly sensitive (95%) and specific (90%–98%) and the stool cultures give a low diagnostic yield in chronic infection, with a sensitivity lower than 50%.[15] However, *Strongyloides* infection could not explain the clinical severity nor the adenopathies, myelofibrosis or the extensive bone lytic lesions. Nevertheless, *Strongyloides* might have contributed to or be the trigger of the severe and prolonged findings in an immunodepressed patient with FP.

In fact, due to clinical suspicion, the magnitude of the eosinophilia's (>20.000×10^9/L) and elevated cobalamin, FP rearrangement was screened on admission, which leads to prompt diagnosis and appropriate therapy with immediate clinical and laboratorial improvement. Imatinib's benefit has been well demonstrated in adult studies[2 4] and paediatric case reports.[9] In this case, 100 mg daily was enough to achieve and maintain clinical and molecular remission. Additionally, although used to prevent a cardiogenic shock, the initial use of systemic steroids might have contributed to the effective and rapid reduction in the eosinophil count.

Currently, there are no consensual recommendations regarding dose or treatment duration after FP negativity, as its discontinuation can lead to relapse.[1] However, no molecular relapse was observed after dose reduction and we plan a slow-dose tapering.

Learning points

- In children, hypereosinophilia (>1500/uL) is rare and should be considered an alert sign.
- In developing countries, eosinophilia most commonly derives from infections but clinicians should be aware of other causes.
- Early recognition and aetiologic evaluation of hypereosinophilia are elementary in light of prognostic and therapeutic implications of clonal eosinophilia, and to mitigate eosinophil-mediated organ damage.
- FIP1L1-PDGFRα+ (FP) individuals suffer typical organ dysfunction with skin, lungs, digestive tract, nervous system and heart involvement. In contrast, myelofibrosis and bone lesions are rare.
- Because FP is rare in children, there are no recommendations about tapering or timing to stop imatinib and thus, case reports are useful.

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