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Bone marrow failure and extramedullary hematopoiesis in McCune-Albright syndrome

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Abstract

In fibrous dysplasia/McCune-Albright syndrome (FD/MAS), bone and bone marrow are, to varying degrees, replaced by fibro-osseous tissue typically devoid of hematopoietic marrow. Despite the extensive marrow replacement in severely affected patients, bone marrow failure is not commonly associated with FD/MAS. We present a 14-year-old girl with FD/MAS, who developed pancytopenia and extramedullary hematopoiesis (EMH) with no identified cause, in the setting of iatrogenic thyrotoxicosis and hyperparathyroidism. Pancytopenia, requiring monthly blood transfusions, persisted despite multiple strategies to correct these endocrinopathies. Due to worsening painful splenomegaly, likely as a result of sequestration, splenectomy was performed. Following splenectomy, pancytopenia resolved and patient has since been transfusion-independent. We report the first detailed case of bone marrow failure and EMH in FD/MAS. The etiology of marrow failure is likely multifactorial and related to the loss of marrow reserve due to extensive polyostotic FD, exacerbated by iatrogenic thyrotoxicosis and hyperparathyroidism.

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Compliance with ethical standards

Conflict of interest None.

Mini Abstract:

A patient with fibrous dysplasia developed bone marrow failure and extramedullary hematopoiesis. The etiology likely involved loss of hematopoietic marrow space and uncontrolled endocrinopathies. Splenectomy was therapeutic.

Introduction

Fibrous dysplasia/McCune-Albright syndrome (FD/MAS) is an uncommon skeletal disorder associated with extraskelatal manifestations, including cafe-au-lait macules and/or hyper-functioning endocrinopathies. FD/MAS arises from postzygotic somatic activating mutations in the α -subunit of the G stimulatory protein, leading to constitutive ligand-independent activation of adenylyl cyclase, and dysregulated cAMP production with downstream physiologic effects [1].

In FD bone, there is proliferation of cells of the osteogenic lineage with impaired ability to differentiate to mature osteoblasts, adipocytes, and hematopoiesis-supporting stroma. Bone marrow is replaced by fibro-osseous tissue, yet bone marrow failure is not commonly associated with FD/MAS. An interesting case of marrow fibrosis with extramedullary hematopoiesis (EMH) in MAS was very recently reported as an image [2]. We report the first detailed case of an adolescent girl with FD/MAS, who developed pancytopenia and EMH in association with uncontrolled endocrinopathies.

Case report

A 14-year-old Caucasian girl was diagnosed with FD/MAS at 1 year of age, after presenting with vaginal bleeding and café-au-lait macules. She was diagnosed with gonadotropin-independent precocious puberty after presenting with vaginal bleeding at age 1. Precocious puberty was treated with letrozole between the ages of 1 and 10. She was continued on letrozole until she was approximately 10 years old, at which time it was withdrawn to allow puberty to progress on its own. She experienced frequent and irregular periods with relatively heavy bleeding occurring 2-3 times per month. At age 12, she was started on combined oral contraceptive pills which achieved control of her monthly menstrual cycles. Other MAS manifestations included hyperthyroidism, severe polyostotic FD, and hypophosphatemia. Hyperthyroidism was treated with methimazole until total thyroidectomy was performed at age 10, followed by levothyroxine replacement for postsurgical hypothyroidism. Fibrous dysplasia was almost panostotic with extensive involvement of the skull, spine, and bilateral upper and lower extremities, associated with moderate bone pain, multiple fractures, impaired mobility, and scoliosis. She underwent multiple orthopedic surgeries, including spinal fusion and intramedullary rod placement in both femora and tibiae (Fig. 1a, b). A 2-year trial of bis-phosphonate therapy for pain control provided minimal relief. Fibroblast growth factor 23 (FGF23)-mediated hypophosphatemic rickets was treated with phosphorus and calcitriol, resulting in secondary hyperparathyroidism.

At age 14, she developed fatigue, lower extremity weakness and inability to walk. Her exam was notable for painful hepatosplenomegaly. On abdominal ultrasound, her spleen measured 19 cm, consistent with splenomegaly according to normative data for age on ultrasound imaging [3, 4]. Laboratory evaluation demonstrated pancytopenia: hemoglobin 7.4 g/dL (11.2–15.7), leukocytes 2.8 K/ μ L (3.98–10.04), and platelets 91 K/ μ L (173–369). Reticulocyte count was elevated between 2.9 and 4.2% (0.5–1.5), reflecting bone marrow activity. On histology, bone marrow obtained from the femur during an osteotomy as surgical waste 2 years prior revealed multiple areas of normal hematopoietic marrow (Fig. 1c, d, e). In contrast, the results of an iliac crest bone marrow biopsy at presentation was hypocellular with only 10% cellularity (Fig. 1f). Liver biopsy revealed significant trilineage EMH (Fig. 1g, h). A thorough hematologic evaluation did not reveal an infectious or oncologic cause of bone marrow failure. The patient's CMV and EBV PCR were negative and there was no evidence of malignancy on the peripheral blood smear. She had appropriate erythropoietin production. There was no evidence of hemolysis as per the patient's negative direct Coombs, as well as normal lactic acid dehydrogenase and haptoglobin. Evaluation for a potential hemoglobinopathy via high-performance liquid chromatography was negative as well. The following iron studies showed low iron 32 mcg/dL (50–120), low transferrin 190 mg/dL (200–360), 12% saturation (20–50%), and high ferritin 290 mcg/L (13–150). Folate 5.7 ng/mL (3.0–17.0) and B12 201 pg/mL (193–982) levels were within normal. Although ferritin can be elevated in iron deficiency as an acute phase reactant, this case is inconsistent with pure iron deficiency anemia. The etiology of elevated ferritin is likely multifactorial, including blood transfusions the patient had already received, potential liver involvement, chronic inflammation, and problem with bone marrow production of red blood cell (RBC) precursors, making her presentation more consistent with anemia of chronic disease. Oral ferrous sulfate therapy was initiated due to superimposed mild iron deficiency, and a monophasic oral contraceptive pill was started, with placebo pills skipped for three consecutive packs, to allow for menstruation every 3 months. The electrolytes and renal function remained within the normal range during pancytopenia. Multiple monthly blood transfusions were required without resolution of symptoms.

At presentation to the National Institutes of Health at age 14, she was clinically hyperthyroid with tachycardia, hypertension, and diarrhea, on levothyroxine 200 mcg/day. Triiodothyronine (T3) was elevated at 349.4 ng/dL (60.0–209.0), with a low free thyroxine (T4) 0.8 ng/dL (0.9–1.7), T4 of 7.5 mcg/dL (4.4–12.2) and suppressed thyroid-stimulating hormone (TSH) < 0.01 mIU/mL (0.76–4.20), consistent with thyrotoxicosis secondary to overtreatment with levothyroxine and increased conversion of T4 to T3 typical of MAS [5]. Initially, the levothyroxine dose was decreased to 100 mcg/day and propylthiouracil (PTU), 100 mg TID for 3 days, was added to acutely reduce the peripheral T4 to T3 conversion. The PTU dose was subsequently increased to 200 mg TID and levothyroxine dose was decreased to 50 mcg/day for an additional 3 days with the improved repeat thyroid function test results: T3 274.6 ng/dL (60.0–209.0) and T4 5.1 mcg/dL (4.4–12.2). PTU was discontinued and levothyroxine was gradually increased to 137 mcg/day over 2 months until T3 was in the normal range.

On admission, while on therapy with elemental phosphorus 250 mg TID, calcitriol 0.25 mcg/day, and cholecalciferol 1000 IU/d, the parathyroid hormone (PTH) was elevated at 100

pg/mL (15–65) with serum calcium 2.26 mmol/L (2.15–2.55), phosphorus 2.4 mg/dL (3.5–4.9), and the 24-h urinary calcium excretion of 3.20 mmol/24 h (1.25–6.25), suggesting secondary hyperparathyroidism either due to suboptimal therapy with phosphate and calcitriol, intermittent compliance, or FGF23 excess. FGF23 (C-terminal) was elevated at 346 RU/mL (< 230) but intact FGF23 was unavailable. Alkaline phosphatase was significantly increased at 1857 U/L (100–320). 25-hydroxyvitamin D was 47 ng/mL and 1,25-dihydroxyvitamin D was 35 pg/mL (24–86). After dose increases in calcitriol and phosphate, both serum calcium (2.09 mmol/L) and urinary calcium excretion (1.29 mmol/24 h) decreased; PTH remained elevated at 72 pg/mL, consistent with secondary hyperparathyroidism and skeletal remineralization. Five months later, on calcitriol 1.25 mcg BID, elemental phosphorus 500 mg TID, calcium carbonate 1.5 g BID, and cholecalciferol 5000 IU/d, PTH was now normal at 35.4 pg/mL (14–72), calcium 9.4 mg/dL (8.5–10.2), and phosphorus 2.7 (3.2–6.3 mg/dL).

Despite multiple strategies to improve pancytopenia over 16 months, painful splenomegaly worsened, requiring splenectomy. Postsurgical pathology of the spleen confirmed the presence of EMH (Fig. 1i). Following splenectomy, all cell counts started to recover (Fig. 2). Eighteen months postsplenectomy, the patient remains clinically stable without pancytopenia. She has required no additional transfusions. Her weakness and fatigue improved significantly.

Discussion

This is the first detailed clinical report of bone marrow failure and EMH in a patient with FD/MAS, demonstrating the complexity and multifactorial etiology of pancytopenia. Typically, patients with polyostotic FD have sufficient hematopoietic stem cells (HSCs) to meet the demands of blood cell production. It is possible that at baseline, this patient's HSCs were barely adequate. Uncontrolled hyperthyroidism and hyperparathyroidism, together with the abnormal marrow environment due to changes in the bone marrow niche as a result of FD and surgical instrumentation, may have been sufficient to induce pancytopenia. We hypothesize that the etiology of pancytopenia is multifactorial and falls into two main categories: (1) loss of hematopoietic marrow space, as a result of FD and surgical instrumentation; and (2) suppression of blood cell production as a result of hyperparathyroidism, thyrotoxicosis, and anemia of chronic disease.

Skeletal stem cells (SSCs), which reside in the postnatal bone marrow provide a niche for hematopoietic progenitor cells [6]. In FD, which is a disease of SSCs, mutant $G\alpha_s$ impairs cellular differentiation, giving rise to an abnormal hematopoietic microenvironment [7]. It is possible that with worsening polyostotic FD and secondary insults, mainly hyperthyroidism and hyperparathyroidism, the marrow hematopoietic niche became compromised, and hematopoiesis was initiated at extramedullary sites. Although there are no reported cases of decreased marrow function as a result of intramedullary rod placement, a partial contribution of surgical instrumentation cannot be definitively ruled out in this rare case without a clear explanation for the etiology of bone marrow failure.

The association between anemia and hyperparathyroidism is well-studied in secondary hyperparathyroidism in chronic kidney disease and is attributed to the replacement of the marrow cavity with fibrous tissue. Proposed mechanisms of anemia include the stimulatory effect of PTH/cAMP on marrow fibroblasts through TNF- α and IL1- β [8], leading to fibrosis and potential direct toxic effect of PTH on RBC production and survival through increased hemolysis [9]. In FD/MAS, ligand-independent, constitutive G α_s /cAMP signaling can lead to dysregulated cAMP signaling and marrow fibrosis. Despite the high prevalence of secondary hyperparathyroidism in FD/MAS, there are no previous reports of bone marrow failure. We did not find such a relationship between PTH and pancytopenia in our large MAS cohort, either.

Pancytopenia is a rare complication of hyperthyroidism, reported in few case reports of untreated Graves' disease, multinodular goiter with thyrotoxicosis, and hyperthyroidism in pregnancy [10–12]. Suspected mechanisms include ineffective hematopoiesis, reduction in blood cell life span, autoimmune processes and toxicity of thyroid hormone, without a clear pathogenesis. In MAS, hyperthyroidism results from both increased hormone production and increased conversion of T4 to T3 [5] presumably occurring in liver, due to effect of hepatic mutated G α_s on the deiodinases. In this patient, hyperthyroidism potentially exacerbated ineffective hematopoiesis.

The severity of both hyperparathyroidism and hyperthyroidism was inconsistent to be the primary driver of anemia. In addition, pancytopenia and EMH persisted and worsened despite correction of hyperparathyroidism and thyrotoxicosis. The lack of a resolution after correction of these endocrinopathies suggests that it is exceedingly unlikely that bone marrow failure was the result of these endocrinopathies alone, but they were possibly modifying factors.

The spleen can become massively and irreversibly enlarged as a newly established site of EMH, yet insufficient to fully replace the marrow hematopoiesis. Compensatory EMH with massive splenomegaly, which was confirmed histologically (Fig. 1i), likely exacerbated pancytopenia, followed by improvement post-splenectomy. The reason for resolution of pancytopenia post-splenectomy remains unclear, but following splenectomy, her cytopenia likely improved as there was no longer splenic sequestration. Given patient's almost panostotic FD, there is no representative area for an adequate bone marrow aspirate to be performed to assess bone marrow activity or reserves. In addition, without a liver biopsy, one cannot definitively conclude that EMH has resolved. Clinically, at this time, the patient appears to be compensated.

In summary, this case identifies pancytopenia with EMH as a novel complication of FD/MAS. The etiology appears to be complex, and without a definitive pathophysiologic explanation. It is a reasonable hypothesis that the cause was multifactorial, including the additional insults of hyperthyroidism and/or hyperparathyroidism. Eventually, splenic sequestration outstripped the splenic contribution to hematopoiesis, and splenectomy allowed for the restoration of hematopoietic homeostasis, at least by resolution of sequestration.

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Fig. 1.

a AP spine film demonstrating severe scoliosis and spinal fusion for correction. **b** AP film of lower extremities with intramedullary rods in the right femur and bilateral tibiae to correct deformities. Note the typical radiographic findings of fibrous dysplasia (FD), including ground glass appearance and thin cortices (black arrow). **c** Bone marrow obtained as surgical waste 2 years prior to pancytopenia. **d** Areas of fibrous tissue (FT), woven bone (WB), and osteoid (o), Masson stain. **e** Evidence of normal hematopoiesis. **f** Iliac crest bone marrow biopsy at the time of presentation with pancytopenia, notable for hypocellularity, Masson

stain, $\times 400$. **g** Liver biopsy, H & E stain, erythroid focus (black arrow) demonstrating extramedullary hematopoiesis. **h** Liver biopsy, anti-CD71 immunostain (black arrow) confirms erythroid precursors. **i** Spleen, postsplenectomy, H & E stain. Encircled are erythroid precursors, indicating extramedullary hematopoiesis

Fig. 2.

Hematology laboratory trend. The patient was noted to have normal values of leukocytes, hemoglobin, and platelets prior to her acute presentation with pancytopenia. She required multiple red blood cell transfusions (double headed arrow) between days 750 and 1100. She underwent splenectomy (black arrow), followed by normalization of her counts. Please note that the patient received packed red blood cell transfusion right before splenectomy in preparation for the surgery; hence the acute increase in her hemoglobin level before splenectomy