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Case Report

Primary hypertrophic osteoarthropathy with myelofibrosis and anemia: a case report and review of literature

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Abstract: Primary hypertrophic osteoarthropathy (PHO) is a rare and usually benign disorder of bone and connective tissue growth. Here we present a 28-year-old male patient presenting to our hospital with PHO and symptomatic anemia. Bone marrow biopsy suggested myelofibrosis, a serious complication of PHO, which is often neglected upon admission, but may lead to life-threatening anemia.

Keywords: Primary hypertrophic osteoarthropathy, myelofibrosis

Introduction

Primary hypertrophic osteoarthropathy (PHO) is a rare disorder characterized by abnormal growth of bone and connective tissue. It is usually considered as a benign disease. However, several cases have reported PHO to be complicated by life-threatening anemia. Various conditions may lead to anemia in PHO patients, including blood loss from the gastrointestinal tract, bone marrow failure and serum erythropoiesis inhibitors [1], among which, myelofibrosis is rare and can be neglected easily, with only 21 cases [1-13] reported according to our knowledge. Here, we present a young male patient with PHO, who may develop fatal anemia due to myelofibrosis.

Case report

A 28-year-old male was admitted to West China Hospital of Sichuan University on February 7, 2014 mainly complaining of recurrent arthralgia for over 10 years, and fatigue for 1 year. When the patient was in his middle school, he felt arthralgia and periarticular soft tissue swelling, which were aggravated by movement. The patient went to several local hospitals and received unclear treatments which did not relieve the symptoms. He was then diagnosed with "rheumatoid arthritis", and was treated by prednisone and NSAIDs for months. The joint pain was slightly relieved, but the patient discontinued the therapy when the enlargement of joints became progressive and obvious. Around 6 years prior to current admission, the skin of his face and scalp became thickened and furrowed progressively (**Figure 1**). One year prior to admission, the patient visited a local hospital because of fatigue and dyspnea. He was diagnosed with "severe anemia", and became better after blood transfusion. About 2 months prior to admission, the patient experienced an obvious exacerbation of arthralgia and fatigue, and was diagnosed with "acromegaly and severe anemia" in a local hospital after examination. Bromocriptine and blood transfusion was given, but symptoms could only be transiently released after therapy. Thus the patient presented to our hospital for further diagnosis and treatment. He did not have previous pulmonary or cardiac disorders. His parents and sister looked normal, and no other family members presented similar appearance. The patient appeared to be older than his real age, with prominent gyrus-like skin folds found in his scalp, forehead, and cheeks, and acne scars found on his oily and sweaty face. He had pale palpebral conjunctiva, and his eyelids, knees, ankles, wrists, knuckles, and toes appeared

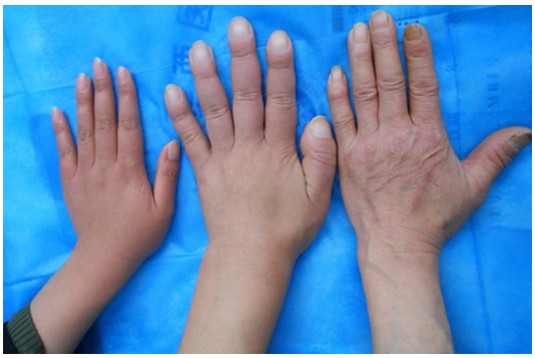

Figure 1. Gyrus-like skin folds of the scalp and face.

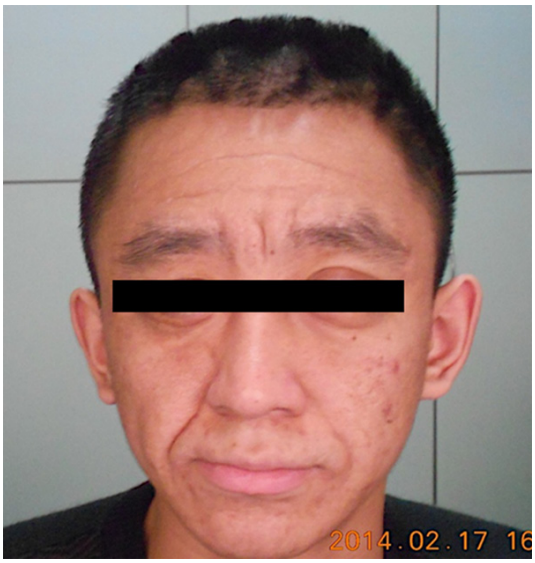

Figure 2. Clubbing fingers can be observed only in the patient. From left to right: the younger sister of the patient, the patient himself and the patient's father.

swelling. Clubbing fingers and toes were obvious bilaterally (**Figure 2**). Superficial lymph nodes were not palpable, and neither was the liver nor spleen. Evaluation of his family history did not reveal any positive result.

After being admitted to the hospital, serum creatine, transaminases, growth hormone, and thyrotropin of the patient were all within the normal range. Growth hormone could be significantly reduced from 0.22 ng/mL to 0.07 ng/mL after a 75-g oral glucose loading. The X-ray indicated that the periosteum and cortex of bones were thickened with rough margin in the bilateral lower limbs, such as the metatarsus, femur, tibia, radius, and other long bones (**Figure 3**). Magnetic resonance imaging (MRI)

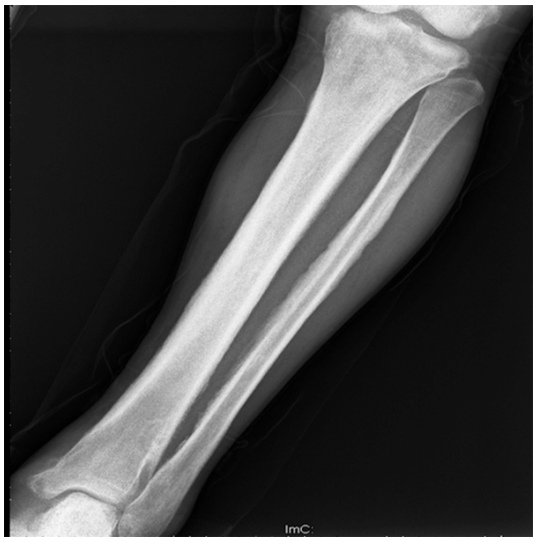

Figure 3. Periosteal reaction in the right tibia and fibula.

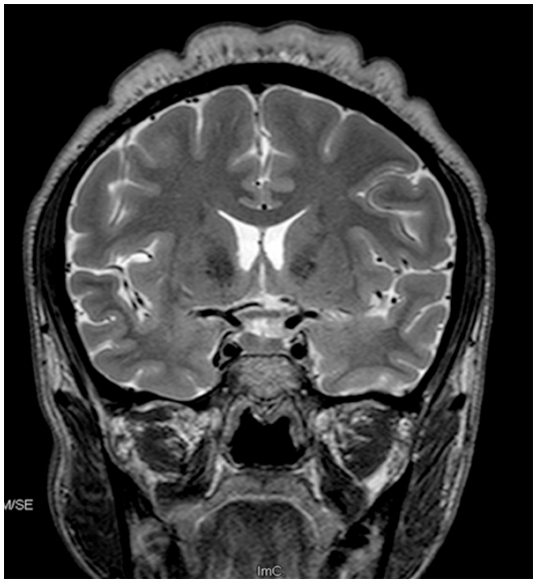

Figure 4. Swelling of soft tissue in the scalp was showed on MRI scan of the head.

indicated swelling of soft tissue in the scalp (**Figure 4**). Endoscopy showed gyrus-like changes in the gastric mucus and multiple polyps in the duodenum. Moreover, the hemoglobin was as low as 68 g/L (normal range: 130-175 g/L), the red blood cell count was 3.09×10^{12}/L (normal range: $4.3\text{-}5.8 \times 10^{12}$/L), the reticulocyte count was 0.0276×10^{12}/L. Occult blood of stool was negative. Erythropoietin level increased greatly to more than 200.00 mIU/ml. Serum iron (11.70 μmol/L), serum iron satura-

Table 1. Summary of reported PHO cases with myelofibrosis

Case No	First Author, Year of Publication	Gender	Ethnicity or Country	Age of PHO Diagnosis	Anemia	Anemia associated symptoms	Treatment	Prognosis
1	Tanaka H, 1991 [1]	M	Japan	26	Y	Fatigue	Methylprednisolone, prednisolone, iron therapy, blood transfusion	Partial control of the symptoms
2	Akoglu H, 2009 [2]	M	Turkey	27	Y	NR	Low dose oral corticosteroid, NSAID	Prolonged remission
3	Arikan S, 2009 [3]	M	Turkey	24	Y	Weakness, dizziness	NR	NR
4	Bachmeyer C, 2005 [4]	M	Algerian	23	Y	NR	Blood transfusion	Lost to follow up
5	Diggle CP, 2012 [5]	M	Hispanic	19	Y	NR	NR	NR
6	Diggle CP, 2012 [5]	M	Hispanic	12	Y	NR	NR	NR
7	Diggle CP, 2012 [5]	M	French	NR	Y	NR	NR	NR
8	Diggle CP, 2012 [5]	M	North African	16	Y	NR	NR	NR
9	Diggle CP, 2012 [5]	M	North African	17	Y	NR	NR	NR
10	Diggle CP, 2012 [5]	M	North African	15	Y	NR	NR	NR
11	Diggle CP, 2012 [5]	M	Dutch	19	Y	NR	NR	NR
12	Diggle CP, 2012 [5]	M	Turkish	NR	Y	NR	NR	NR
13	Fontenay-Roupie M, 1995 [6]	M	France	46	Y	NR	NR	NR
14	Kumar U, 2008 [7]	M	India	26	Y	Easy fatigue	NR	NR
15	Neufeld KR, 2009 [8]	M	US	61	Y	NR	No specific treatment	Asymptomatic upon admission
16	Ninomiya S, 2011 [9]	M	Japan	21	Y	NR	Blood transfusion, prednisolone (30 mg/day, p.o.)	Prolonged remission
17	Saghafi M, 2008 [10]	M	Iran	43	Y	NR	Low dose of prednisolon, omeprasol, ferrous sulfate and folic acid	Partial control of the symptoms
18	Saigal R, 2009 [11]	M	India	32	Y	Easy fatigue	Routine hematinics	NR
19	Venencie PY, 1988 [12]	M	France	35	Y	NR	NR	NR
20	Yu SJ, 1994 [13]	M	Caucasian	64	NR	NR	Corticosteroids	Prolonged remission
21	Yu SJ, 1994 [13]	F	Caucasian	71	NR	NR	Partial resection of the medial meniscus and lateral patellar retinacular	NR
22	Current case	M	China	28	Y	Fatigue	No specific treatment	Lost to follow up

tion (49.2%) and lactate dehydrogenase (132 IU/L) were all within normal range, while the total iron binding capacity decreased to 23.80 μmol/L, and the serum ferritin increased to 627.90 ng/mL (normal range: 24-366 ng/mL). The direct antiglobulin test and hemoglobin electrophoresis were both normal. Tumor marker test came back negative. Bone marrow aspiration yielded dry taps, with 60% granulocyte and 2% erythrocyte. Bone marrow biopsy suggested myelofibrosis. The bone mineral densities of the neck of femur, the hip bone and the lumbar vertebrates 1-4 were 1.032 g/cm^2 (Z-value: 0.5), 1.206 g/cm^2 (Z-value: 1.7) and 1.127 g/cm^2 (Z-value: 0.5), respectively. Therefore, the patient was diagnosed with PHO and myelofibrosis. However, the patient refused to take any further treatment after diagnosis, and was discharged against doctors' advice.

Discussion

PHO is a rare genodermatosis [14], and is poorly recognized. Although the pathogenesis of PHO associated with myelofibrosis is still disputed, the fibroblastic proliferation has been suggested to be stimulated by various mediators, such as PDGF, TGF-beta 1 and VEGF, released from platelets and megacaryocyte alpha-granules [12]. It presents as clubbing of the fingers, periostitis of bones, and synovitis of the joints. It should be differentiated with secondary hypertrophic osteoarthropathy due to neoplasm, pulmonary or cardiac disorders. Myelofibrosis is rarely occurred and usually omitted in PHO patients. Including our case, only 22 PHO cases with myelofibrosis [1-13] have been reported to date according to our knowledge (shown in **Table 1**). Among those patients, 21 (94.5%) were male, and 9 (40.9%) were reported from Asian countries. Anemia associated symptoms were reported in only 5 (22.7%) patients. Anemia, sometimes also leucopenia, would present as the result of myleofibrosis. As anemia could also be fatal, PHO is suggested to be in an advance phase when complicated by myelofibrosis [1].

Anemia usually develops gradually and together with other symptoms as PHO progresses. Some patients can even go with very low hemoglobin levels but be absent of symptoms of anemia [12]. Although our patient had a long history of PHO, fatigue and other anemia-associated symptoms didn't develop obviously until the recent 1 year, suggesting that at the very beginning of the disease, hematopoiesis could be affected but well compensated.

Although the pathogenesis of PHO remains unclear, associated myelofibrosis is thought to be a consequence of overgrowth of the normal marrow matrix, due to the disorder of various growth factors, such as von Willebrand factor, etc [15]. All these changes reduce hematopoiesis in the marrow. Some genetic work has been done to help identify PHO patients at risk of myelofibrosis. A recent analysis suggested that PHO patients with prostaglandin transporter SLCO2A1 mutations were more likely to develop myelofibrosis [5].

No standard treatment for myelofibrosis in PHO patients has been established so far. Patients with severe anemia can be treated with blood transfusion, which may sometimes be the only way to improve the condition, but not to cure the disease [9]. Steroid treatment was used in several cases. A 21-year-old PHO patient was reported to be successfully treated by prednisolone (0.5 mg/kg/day) [9], as for primary myelofibrosis, while a 19-year-old PHO patient with iron deficiency was treated by steroid pulse and iron therapy and achieved improvement in hemoglobin level [1].

During current admission to our hospital, the patient refused to receive any treatment and was directly discharged after diagnosis. However, if bone marrow biopsy was previously screened for this patient, we might be able to acquire a better knowledge of his prognosis earlier and take action accordingly.

Although PHO is primarily a benign disorder, we highly suggest regular and careful monitor of bone marrow and hematopoietic conditions in addition to other regular tests, such as blood cell count, when approaching suspected patients, to avoid missing the diagnosis of myolefibrosis, which is very likely to progress into fatal anemia.

Disclosure of conflict of interest

None.

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References

[1] Tanaka H, Maehama S, Imanaka F, Sakai A, Abe K, Hamada M, Yamashita J, Kimura A, Imamura N, Fujimura K. Pachydermoperiostosis with myelofibrosis and anemia: report of a case of anemia of multifactorial causes and its improvement with steroid pulse and iron therapy. Jpn J Med 1991; 30: 73-80.

[2] Akoglu H, Akoglu G, Yuksel C, Dede F, Yenigun EC, Ozturk R, Gonul II, Erekul S, Odabas AR. Pachydermoperiostosis with myelofibrosis and renal amyloid A amyloidosis. J Clin Rheumatol 2009; 15: 414-416.

[3] Arikan S, Sen I, Bahceci M, Tuzcu A, Ayli M. An interesting case of pachydermoperiostosis with idiopathic myelofibrosis associated with monosomy 22. Int J Dermatol 2009; 48: 882-885.

[4] Bachmeyer C, Blum L, Cadranel JF, Delfraissy JF. Myelofibrosis in a patient with pachydermoperiostosis. Clin Exp Dermatol 2005; 30: 646-648.

[5] Diggle CP, Parry DA, Logan CV, Laissue P, Rivera C, Restrepo CM, Fonseca DJ, Morgan JE, Allanore Y, Fontenay M, Wipff J, Varret M, Gibault L, Dalantaeva N, Korbonits M, Zhou B, Yuan G, Harifi G, Cefle K, Palanduz S, Akoglu H, Zwijnenburg PJ, Lichtenbelt KD, Aubry-Rozier B, Superti-Furga A, Dallapiccola B, Accadia M, Brancati F, Sheridan EG, Taylor GR, Carr IM, Johnson CA, Markham AF, Bonthron DT. Prostaglandin transporter mutations cause pachydermoperiostosis with myelofibrosis. Hum Mutat 2012; 33: 1175-1181.

[6] Fontenay-Roupie M, Dupuy E, Berrou E, Berrou E, Tobelem G, Bryckaert M. Increased proliferation of bone marrow-derived fibroblasts in primitive hypertrophic osteoarthropathy with severe myelofibrosis. Blood 1995; 85: 3229-3238.

[7] Kumar U, Bhatt SP, Misra A. Unusual associations of pachydermoperiostosis: a case report. Indian J Med Sci 2008; 62: 65-68.

[8] Neufeld KR, Price K, Woodward JA. Massive eyelid thickening in pachydermoperiostosis with myelofibrosis. Ophthal Plast Reconstr Surg 2009; 25: 316-318.

[9] Ninomiya S, Hara T, Tsurumi H, Kanemura N, Kasahara S, Ogawa Y, Seishima M, Hirose Y, Moriwaki H. Myelofibrosis successfully treated with prednisolone in a patient with pachydermoperiostosis. Intern Med 2011; 50: 2207-2211.

[10] Saghafi M, Azarian A, Nohesara N. Primary hypertrophic osteoarthropathy with myelofibrosis. Rheumatol Int 2008; 28: 597-600.

[11] Saigal R, Kansal A, Mittal M, Singh Y, Ram H. Pachydermoperiostosis with myelofibrosis and empty sella. J Assoc Physicians India 2010; 58: 253-255.

[12] Venencie PY, Boffa GA, Delmas PD, Verola O, Benkaïdali I, Frija J, Pillet B, Puissant A. Pachydermoperiostosis with gastric hypertrophy, anemia, and increased serum bone Gla-protein levels. Arch Dermatol 1988; 124: 1831-1834.

[13] Yu JS, Greenway G, Resnick D. Myelofibrosis associated with prominent periosteal bone apposition. Report of two cases. Clin Imaging 1994; 18: 89-92.

[14] Castori M, Sinibaldi L, Mingarelli R, Lachman RS, Rimoin DL, Dallapiccola B. Pachydermo periostosis: an update. Clin Genet 2005; 68: 477-486.

[15] Matucci-Cerinic M, Martinez-Lavin M, Rojo F, Fonseca C, Kahaleh BM. von Willebrand factor antigen in hypertrophic osteoarthropathy. J Rheumatol 1992; 19: 765-767.