Case Report

Autoimmune hemolytic anemia diagnosed in a Thai woman with limited cutaneous systemic sclerosis

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Abstract:

Although systemic sclerosis (SSc) and auto-immune hemolytic anemia (AIHA) both have an auto-immune process as the underlying pathogenesis, AIHA has been still rarely reported among patients who have SSc to date. This report presents a case of AIHA that was accidentally found in a Thai woman who presented the clinical features of limited cutaneous systemic sclerosis (lcSSc). She was a 54-year-old Thai patient presenting tenseness, darkness, mild swelling and minimal pain of all fingers and toes for a few months, without fever or weight loss. The physical examination showed pallor of the conjunctivae, hardening and darkening of skin of all fingers and toes and sclerodactyly with stiffness of the fingers and toes. Her blood tests showed: Hb 10.6 g/dL, WBC 10,860/mm^3, platelet 452,000/mm^3, MCV 81.9 fl, positive direct anti-globulin test 3+, positive ANA, homogeneous type 1,280, speckled type 320, nucleolar type 320, positive anti-Scl-70 IgG antibodies, erythrocyte sedimentation rate (ESR) 94 mm/hr, negative for anti-RNP, anti-double stranded DNA, anti-Smith, anti-CCP antibodies and rheumatoid factor. The urinalysis and chest film showed unremarkable study. She was clinically diagnosed as having co-incidence of AIHA and lcSSc, and was treated with oral prednisolone, cyclophosphamide and chloroquine. AIHA as well as lcSSc responded well to immuno-suppressive therapy; Hb was up to 12.7 g/dL and she could make a fist in 10 weeks. Although anemia generally seemed to be a poor prognostic factor among patients with SSc alone, SSc with AIHA seemed to respond to therapy better than SSc alone that looked similar to SSc in an overlap syndrome with other systemic autoimmune diseases.

Keywords : ● *Autoimmune hemolytic anemia* ● *Limited cutaneous systemic sclerosis*

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รายงานผู้ป่วย

โรคโลหิตจางจากการที่เม็ดเลือดแดงแตกเนื่องจากภูมิคุ้มกันต่อต้านตนเอง ที่วินิจฉัยได้ในผู้ป่วยหญิงไทยที่มีโรคหนังแข็งตามระบบแต่มีรอยโรคจำกัด

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บทคัดย่อ

แม้ว่าทั้งโรคหนังแข็งตามระบบ หรือ SSc และ โรคโลหิตจางจากการที่เม็ดเลือดแดงแตกเนื่องจากภูมิคุ้มกันต่อต้านตนเอง หรือ AIHA ต่างก็มีขบวนการภูมิคุ้มกันต่อต้านตนเอง เป็นภูมิหลังในทางพยาธิกำเนิด แต่จนปัจจุบันนี้ โรคโลหิตจางจากการที่เม็ดเลือดแดงแตกเนื่องจากภูมิคุ้มกันต่อต้านตนเองในผู้ป่วยโรคหนังแข็ง ยังมีรายงานน้อยมาก วัตถุประสงค์ของรายงานนี้ คือ นำเสนอผู้ป่วยโรคโลหิตจางจากการที่เม็ดเลือดแดงแตกเนื่องจากภูมิคุ้มกันต่อต้านตนเอง ที่บังเอิญพบในผู้ป่วยหญิงไทยที่มีลักษณะทางคลินิกแบบโรคหนังแข็งแบบมีรอยโรคจำกัด ซึ่งเป็นผู้ป่วย อายุ 54 ปี ที่มาพบแพทย์ด้วยอาการบวมเล็กน้อยร่วมกับอาการผิวหนังตึง คล้ำ ของนิ้วมือ นิ้วเท้าทุกนิ้ว และอาการเจ็บบ้างเล็กน้อย เป็นเวลาประมาณ 2-3 เดือน โดยไม่มีไข้ น้ำหนักไม่ลด ตรวจร่างกาย พบว่าผิวหนังที่นิ้วมือนิ้วเท้าทุกนิ้ว คล้ำ แข็ง และ นิ้วมือแข็งกำมือได้ไม่เต็มที่ (sclerodactyly) ตรวจเลือดพบว่า Hb 10.6 กรัม/ดล, WBC 10,860/มม^3, platelet 452,000/มม^3, MCV 81.9 เฟมโตลิตร, ตรวจ direct anti-globulin test ให้ผล 3+, ตรวจ ANA ให้ผลบวก โดยชนิด homogeneous type 1,280, speckled type 320, nucleolar type 320, ตรวจ anti-Scl-70 IgG antibodies ให้ผลบวก, ESR 94 มม/ชม., ตรวจ anti-RNP, anti-double stranded DNA, anti-Smith, anti-CCP antibodies และ rheumatoid factor ให้ผลลบทั้งหมด ให้การวินิจฉัยว่า เป็นโรคโลหิตจางจากการที่เม็ดเลือดแดงแตกเนื่องจากภูมิคุ้มกันต่อต้านตนเอง ร่วมกับ โรคหนังแข็งตามระบบแต่มีรอยโรคจำกัด ให้การรักษาด้วย prednisolone, cyclophosphamide และ chloroquine รับประทาน ทั้งโรคโลหิตจางจากการที่เม็ดเลือดแดงแตกเนื่องจากภูมิคุ้มกันต่อต้านตนเอง และ โรคหนังแข็ง ตอบสนองต่อการรักษาด้วยยากดภูมิต้านทานเหล่านี้ด้วยดี ฮีโมโกลบินเพิ่มเป็น 12.7 กรัม/ดล และ กำมือได้ดี แม้ว่าภาวะโลหิตจางโดยทั่วไปจะเป็นปัจจัยลบในการพยากรณ์โรคผู้ป่วยโรคหนังแข็ง แต่โรคหนังแข็ง ที่พบร่วมกับโรคโลหิตจางจากการที่เม็ดเลือดแดงแตกเนื่องจากภูมิคุ้มกันต่อต้านตนเอง กลับดูตอบสนองต่อการรักษาดีกว่าผู้ป่วยโรคหนังแข็งตามระบบอย่างเดียว ซึ่งดูคล้ายกับผู้ป่วย โรคหนังแข็ง ที่มีโรคภูมิคุ้มกันต่อต้านตนเองอื่นๆ ร่วมด้วย ที่เรียกว่า กลุ่มอาการ overlap

คำสำคัญ : ● *โรคโลหิตจางจากการทีเม็ดเลือดแดงแตกเนืองจากภูมิคุ้มกันต่อต้านตนเอง*

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วารสารโลหิตวิทยาและเวชศาสตร์บริการโลหิต. 2563;30:399-403.

Introduction

Systemic sclerosis (SSc) is a chronic multisystem auto-immune disease, characterized by thickness and fibrosis due to the accumulation of collagen tissue and damage of the small vessels of mainly the skin, and other visceral organs such as the heart, lungs, kidneys or gastro-intestinal tract[1]. The preponderant sites of the skin involved are the hands and feet resulting in swollen and stiffness of the fingers, sclerodactyly and finally arachnodactyly. Other clinical skin manifestations include Raynaud's phenomenon, hyper and/or hypopigmented macules and telangiectasia. Its common, associated autoantibodies consist of anti-Scl 70 and anti-centromere antibodies which are very useful for distinguishing patients with SSc from normal control and other auto-immune disease patients although both have sensitivity around 32 to 34%[2,3]. SSc is divided into lcSSc if lesions involve only the hands, feet and face and diffuse cutaneous systemic sclerosis (dcSSc) if lesions extend above the elbows, knees and chest[4].

SSc may be found co-existing with other auto-immune diseases either systemic such as Sjogren syndrome, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) or localized such as thyroiditis, myositis and primary biliary cirrhosis (PBC)[5]. However, the co-existence of SSc and AIHA has been rarely found[6] since 1955 in which the first case was recognized[7]. Among most cases, AIHA has usually been found complicating cases of SSc. In contrast, AIHA emerging concurrently with SSc or preceding SSc has been rarely found[8,9]. This report aimed to present a case that had both SSc and AIHA concurrently.

Case Report

A 54-year-old Thai woman had skin thickness with mild swelling and minimal pain of all fingers and toes for a few months. In addition, she noticed the skin of all her fingers and toes became gradually darker. She did not present fever or weight loss. Besides mild pallor without jaundice and hepatosplenomegaly, the physical examination reconfirmed firm to hard, dry and dark skin of the dorsum side of all fingers, toes and face, sclerodactyly, mild stiffness of the fingers and she could not make a full fist of both hands, but no definite arthritis was observed at any finger. Other body parts were found unremarkable.

The initial blood tests revealed Hb 10.6 g/dL, Hct 29.5%, WBC 10,860/mm^3, N 48.5%, L 44.6%, platelet 452,000/mm^3, MCV 81.9 fl, MCH 29.4 pg, MCHC 35.9 g/dL, RDW 19.9%, corrected reticulocyte count 3.2%, rheumatoid factor-negative, normal thyroid function, ESR 94 mm/hr, direct anti-globulin test -positive 3+, indirect anti-globulin test -positive 1+,

FBS 93 mg/dL, BUN 10.9 mg/dL, creatinine 0.6 mg/dL, albumin 4.2 g/dL, globulin 3.2 g/dL, indirect bilirubin 2.1 mg/dL, direct bilirubin 0.8 mg/dL, AST 33 U/L, ALT 19 U/L, alkaline phosphatase 56 U/L, normal serum electrolyte, anti-cyclic citrulinated peptide (CCP)-negative, anti-RNP -negative, anti-Scl-70 IgG- positive, ANA-positive; homogeneous 1:1,280, speckled 1:320, nucleolar 1:320, anti-cytoplasmic -negative, anti-double stranded DNA-negative and anti-Smith-negative.

The urinalysis and the chest film study were unremarkable while the ultrasonography of the whole abdomen showed only mild fatty liver.

She was clinically diagnosed as concurrently having lcSSc and AIHA and regularly treated with oral prednisolone 60 mg, chloroquine, naproxen for joint pain and cyclophosphamide 50 mg because SLE could not be completely excluded. Ten weeks later, the stiffness and pain of all fingers and toes completely disappeared and she could make a full fist with both hands well although the sclerodactyly and darkness of skin persisted. Her blood tests showed: Hb 12.7 g/dL, WBC 12,220/mm^3, platelet 440,000/mm^3, the direct anti-globulin test 3+ and ESR 52 mm/hr. Prednisolone was gradually tapered off every two weeks, finally stopped and only cyclophosphamide was administered. The stiffness or pain of all fingers and toes never recurred during one year follow-up; her hemoglobin concentration could be kept between 11.4 g/dL and 11.9 g/dL, whereas the direct anti-globulin test was persistently positive.

Discussion

The diagnosis of lcSSc in our patient was exclusively based on the puffy fingers and sclerodactyly and the positivity of anti-Scl 70 antibody[10] that is helpful for distinguishing SSc from other systemic auto-immune diseases[2]. Because her blood tests were found negative for anti-RNP, anti-dS DNA, anti-Smith, and anti-CCP, the mixed connective tissue disease and the overlap syndrome between SSc and other common auto-immune diseases especially SLE and rheumatoid arthritis were less likely[11]. Likewise, the diagnosis of AIHA was based on the positivity of the direct anti-globulin test in the patient with increased reticulocyte count and increased indirect bilirubinemia [12].

Although both AIHA and SSc have an auto-immune process as the common basic pathogenesis, AIHA in cases of SSc has been rarely reported, around 20 cases to date[6,13]. In contrast, AIHA is much more commonly found in other auto-immune diseases particularly SLE, around 5 to 10% of cases[14].

Among 40 patients with scleroderma in the overlap syndrome, dermatomyositis was the most common (19 cases), Sjogren's syndrome (17 cases), RA (6 cases) and SLE (2 cases)[15]. Regarding polyauto-immunity, the organ specific auto-immune diseases, commonly found in SSc, consist of auto-immune thyroid disease (23.1%), Sjogren's syndrome (14.8%), PBC (5.2%) and multiple autoimmune syndrome (MAS), the presence of at least three autoimmune diseases in one individual, 9.7%[16]. Likewise, among 68 Thai patients presenting scleroderma-overlap syndrome, three common concurrent autoimmune diseases comprised polymyositis (70.6%), SLE (16.2%) and RA (13.2%)[17]. AIHA was not found in both series. –

One predisposing factor of SSc is genetic background, e.g., 4q24 in SSc was associated with SLE, PBC, multiple sclerosis and ulcerative colitis, and 12q13.2 in SSc was associated with type 1 diabetes mellitus[18]. However genetic background was unexplored in our case.

In SSc, anemia is a significant poor prognostic factor,[19] but when SSc is complicated by AIHA, as seen in our patient, it responds well to immunosuppressant: skin thickness will improve after cyclophosphamide therapy[20] and AIHA will be in remission despite persistence of a positive direct anti-globulin test result[21]. This looks similar to SSc in the overlap syndrome[22]. Furthermore, internal organ involvement is found in SSc more commonly than in SSc-overlap syndrome[23]. Hence when a patient with SSc is encountered, other auto-immune diseases should be searched to provide a better prognosis.

In a systematic review, high dose of corticosteroid among patients with SSc was found associated with scleroderma renal crisis[24] but was considerably beneficial for AIHA. However, after the hemoglobin could be raised to normal level, prednisolone administration was expected to stop within less than six months despite the persistently positive direct anti-globulin test result[25].

Conclusion

A 54-year-old Thai woman had the co-existence of AIHA and lcSSc that responded well to immunosuppressants: hemoglobin level increased and the hardening skin softened. It suggested SSc with AIHA appears similar to SSc with other auto-immune disease or the overlap syndrome, viz., had better prognosis than SSc alone.

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