Lymphoma in a Patient with Adult Onset Still's Disease Refractory to Immunosuppressants

Priscilla Wong and Lai-Shan Tam

Abstract: Adult onset Still's disease (AOSD) is a rare systemic inflammatory disorder of unknown etiology. Malignancy is one of the important differential diagnoses of AOSD. A 49-year-old man who was diagnosed with AOSD according to the diagnostic criteria of Yamaguchi had refractory response to different kinds of immunosuppressants. Eight months later he developed acute hepatic failure and was subsequently found to have diffuse large B cell lymphoma. This case illustrates the importance of including paraneoplastic syndrome in the differential diagnosis of AOSD; and the continual surveillance of malignancy especially in cases refractory to immunosuppressive therapy.

Keywords: Adult onset Still's disease, lymphoma

Case Report

A 46-year-old man with good past health presented to a private doctor in May 2008 with on and off fever and multiple joint pain for 2 months. He was diagnosed to have early rheumatoid arthritis and was started on methotrexate 7.5 milligram (mg) weekly in May 2008. Despite on methotrexate, he was admitted in December 2008 for high spiking fever with temperature up to 40 degrees Celsius, sore throat, pleuritic chest discomfort, multiple joint pain and swelling for 2 weeks. There was no skin rash, weight loss or night sweat. On physical examination, there were decreased breath sound over the right lower zone of the lungs and bilateral knee swelling. No organomegaly. No lymph nodes were palpable. Laboratory findings showed marked leukocytosis (white blood cell 26.5 x 10^9/L, reference range 4.0-10.8 x 10^9/L) with neutrophils predominance (87%, reference range 41-73%), elevated bilirubin (18 umol/L, reference range <15 umol/L), alkaline phosphatase (238 IU/L, reference range 35-100 IU/L), erythrocyte sedimentation rate (ESR, 101 mm/hr, reference range <10 mml/hr) and C-reactive protein (CRP, 275 mg/L, reference range <9.9 mg/L). The serum ferritin level was 1369 pmol/L (normal 67-889 pmol/L). Rheumatoid factor (RF), antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody were negative. Serological studies for hepatitis B and C and human immunodeficiency virus were all negative. Tumour markers including alpha fetoprotein, carcinogenic embryonic antigen and prostate specific antigen were within normal limit. Chest X-ray showed moderate amount of right pleural effusion. Aspiration of the right pleural fluid reviewed that it was exudative with negative culture and cytology. The right pleural biopsy showed no granulomatous lesion or malignancy. Bronchoscopy with broncho-alveolar lavage was unremarkable. Ultrasound of the abdomen showed mild hepato-splenomegaly only. Gallium scintigraphy showed enhanced marrow and splenic uptake, markedly active polyarthritis involving bilateral shoulders, elbows, wrists, hips, knees, left ankle, bilateral intertarsal joints; and extra-articular manifestations including ocular, pericardial and pleural inflammatory process. There was also diffuse hepatic dysfunction and probably myopathy in the shoulder and pelvic girdle musculature.

Based on the Yamaguchi criteria[1] of fever of at least 39°C for more than 1 week, arthritis lasting more than 2 weeks, leukocytosis with at least 80 percent granulocytes, sore throat, hepatomegaly, splenomegaly, deranged liver function studies, negative tests for ANA and RF, a diagnosis of adult onset Still's disease (AOSD) was made. Prednisolone 7.5 mg daily and methotrexate 15 mg weekly were started in January 2009.

The Department of Medicine & Therapeutics, Prince of Wales Hosptial, Shatin, N.T., Hong Kong SAR

Priscilla Wong MBChB, MRCP

Lai-Shan Tam MBChB, MD(CUHK), FRCP(Glasy)

Correspondence to: Priscilla Wong

In February, there was still multiple joint pain and swelling, together with fever up to 38 degrees Celcius. Prednisolone was titrated up to 20 mg daily. In May, he suffered from recurrent fever, polyarthralgia and sore throat when prednisolone was tapered to 12.5 mg daily while methotrexate was maintained on 15 mg weekly. Blood results showed persistently raised white blood cells, ESR and CRP. Leflunomide was started yet he developed elevated alanine aminotransferase (126 IU/L, reference range <58 UI/L) 1 month after and the drug was stopped. In June, sulphasalazine was given yet there was no clinical response after 5 weeks of treatment. In July, cyclosporin A was started. Meanwhile he required a minimum dose of 25 mg of prednisolone together with non-steroidal anti-inflammatory drug and tramadol for the control of his joint pain and fever. Repeated sepsis work-up in the interim of drug titration were all negative.

In August, he developed sudden onset of right upper quadrant pain and jaundice. A whole-body [^{18}F] fluorodeoxyglucose-positron emission tomography-computed tomography (PET-CT) scan showed multiple liver lesions and multiple hypermetabolic nodes in portal, pancreatic, superior mesenteric artery, pre-aortic and pre-caval region with suspicious metastasis in left lingular lobe. Bone marrow trephine biopsy showed abnormal large cell infiltration with CD20 positive and CD30 negative. Liver biopsy showed the hepatocytes were infiltrated by sheets of moderately pleomorphic cells with prominent nucleoli. The tumour cells were positive for LCA and L26 (CD20) stains. These findings were consistent with diffuse large B-cell lymphoma. He was then transferred to the oncology ward and underwent chemotherapy including cyclophosphamide, vincristine, adriamycin and prednisolone. His fever had completely subsided since after the second course of chemotherapy. There was only one small hand joint with mild tenderness and swelling. After the diagnosis of diffuse large B-cell lymphoma was made, serum glycosylated ferritin was measured. The result was 59%.

Discussion

AOSD is a rare systemic inflammatory disorder of unknown etiology, characterized by quotidian spiking fever with an evanescent rash, arthritis and multiorgan involvement.[2] The disease lacks specific clinical, laboratory and histological features; and the diagnosis is made by the exclusions of infections, malignancies and other rheumatic diseases.

Serum ferritin has been used as a diagnostic and disease activity markers for AOSD.[3,4] It is intimately involved in inflammatory processes. Inflammation is associated with increased production of ferritin by the histiocyte-macrophage system and/or increased release from damaged hepatocytes. Several cytokines mainly IL-1β, IL-18, TNF-α and IL-6, seem to drive the increased production of ferritin. Ferritin levels in AOSD are usually higher than those found in patients with other autoimmune or inflammatory diseases. The validity of hyperferritinaemia as a diagnostic tool was evaluated in a retrospective French study[4] with 49 patients, where a fivefold increase in serum ferritin had 80% sensitivity and 41% specificity; similarly in a Japanese study[1] with 82% sensitivity and 46% specificity. The usefulness of serum ferritin is limited by its low specificity. Very high levels can also be seen in other disease such as liver disease (haemochromatosis, Gaucher's disease), infections (sepsis, HIV), malignancies (leukaemia, lymphoma), and especially in the haemophagocytic syndrome.

A more specific diagnostic marker than ferritin may be its glycosylated fraction.[5] In healthy subjects, 50-80% of ferritin is glycosylated, a process that provides protection from proteolytic enzymes. In inflammatory diseases, saturation of glycosylation mechanisms causes the glycosylated fraction to drop to 20-50%. This phenomenon is particularly relevant in AOSD, since the glycosylation of ferritin is often <20%. However, glycosylated ferritin cannot be used to monitor disease activity or response to treatment, as it remains low for many months after the disease goes into remission. When combined with a fivefold serum rise in ferritin, the sensitivity for the diagnosis of AOSD fell to 43% and specificity rose to 93%.[4]

There are two questions worth discussing in this patient. First whether the development of lymphoma in a patient with AOSD is just a coincidence? Second, is AOSD a paraneoplastic manifestation of the underlying large B cell lymphoma? The absence of lymphadenopathy, both clinically and radiologically in the initial course of the disease had made the suspicion of lymphoproliferative disorder low and the diagnosis difficult. Given with the relatively short time lag

(8 months) between the diagnosis of AOSD and B cell lymphoma, together with the normal glycosylated ferritin level, it is likely that the arthritis and high fever were the initial symptoms of the lymphoma. AOSD has been reported as a paraneoplastic syndrome associated with breast cancer, bronchial carcinoma, laryngeal carcinoma, lymphoma, esophageal cancer and papillary thyroid carcinoma.[6-12] It is usually diagnosed before or concomitantly with the underlying malignancy. These patients were either partially responsive to the treatment for AOSD or had recurrent symptoms after the immunosuppressive therapies were tapered, in which their disease course were quite similar to that in our patient.

This case illustrates the importance of including paraneoplastic syndrome in the differential diagnosis of AOSD; and the continual surveillance of malignancy especially in cases refractory to immunosuppressive therapy. The glycosylated fraction of ferritin which is a more specific marker of AOSD than ferritin may aid the diagnosis, but further studies are needed to confirm its specificity before considering the use as a diagnostic tool in suspected AOSD.

References

1. Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424-30.
2. Pouchot J, Sampalis JS, Beaudet F, et al. Adult onset Still's disease: Manifestations, disease course and outcome in 62 patients. Medicine (Baltimore) 191;70:118-36.
3. Fautrel B. Ferritin levels in adult Still's disease: any sugar? Joint Bone Spine 2002;69:355-7.
4. Fautrel B, Le Moël G, Saint-Marcoux B, et al. Diagnostic value of ferritin and glycosylated ferritin in adult onset Still's disease. J Rheumatol 2001;28:322-9.
5. Vignes S, Le Moël G, Fautrel B, Wechsler B, Godeau P, Piette JC. Percentage of glycosylated serum ferritin remains low throughout the course of adult onset Still's disease. Ann Rheum Dis 2000;59:347-50.
6. Komano Y, Kubota T, Wakabayashi S, et al. A case of paraneoplastic syndrome mimicking adult-onset Still's disease. Mod Rheumatol 2004:14:410-3.
7. Neishi J, Tsukada Y, Maehara T, Ueki K, Maezawa A, Nojima Y. Adult Still's disease as a paraneoplastic manifestation of breast cancer. Scand J Rheumatol 2000;29:328-30.
8. Trotta F, Dovigo L, Scapoli G, Cavazzini L, Castoldi G. Immunoblastic malignant lymphoma in adult onset Still's disease. J Rheumatol 1993:20:1788-92.
9. Sono H, Matsuo K, Miyazato H, et al. A case of adult-onset Still's disease complicated by non-Hodgkin's lymphoma. Lupus 2000;9:468-70.
10. Otrock ZK, Hatoum HA, Uthman IW, Taher AT, Saab S, Shamseddine AI. Non-Hodgkin's lymphoma in a woman with adult-onset Still's disease: a case report. J Med Case Reports 2008;2:73.
11. Kato T, Tanabe J, Kanemoto M, Kobayashi C, Morita S, Karahashi T. A case of extranodal NK/T-cell lymphoma, nasal type mimicking typical manifestations of adult-onset Still's disease (AOSD) with hemophagocytic syndrome: diagnostic consideration between malignant lymphoma without lymphadenopathy and AOSD. Mod Rheumatol 2009 Jul 17. [Epub ahead of print].
12. Ahn JK, Oh JM, Lee J, Kim SW, Cha HS, Koh EM. Adult onset Still's disease diagnosed concomitantly with occult papillary thyroid cancer: paraneoplastic manifestation or coincidence? Clin Rheumatol 2009 Oct 22. [Epub ahead of print]