Rubella infection in adult onset Still's disease

The aetiology of adult onset Still's disease remains unknown although some authors have tried to relate it to a viral infection.[1–10] We describe here a case of typical adult onset Still's disease with a seroconversion in the rubella antibody titre to emphasise that it is probably more than a coincidental event.

A 26 year old woman was admitted because of fever with chills, a pruritic rash, myalgia, sore throat and headache. At the time of physical examination the temperature was 40°C and the pulse rate 104 beat/min. The rash consisted of small pruritic macules over back, periorbicular, legs and arms. The pharynx was erythematous. Some small cervical lymphadenopathies were detected. The leucocyte count was 42.3×10^9 cells/l (93.2% neutrophils) and the haemoglobin concentration was 79 g/l. Liver enzymes were slightly increased, aspartate aminotransferase (AST) 0.80 μkat/l and alanine aminotransferase (ALT) 0.73 μkat/l, but increased to AST 11.77 μkat/l and ALT 7.68 μkat/l after acetylsalicylic acid administration. Lactate dehydrogenase was 17.33 μkat/l. The serum albumin concentration was 26 g/l and the erythrocyte sedimentation rate 60 mm 1st h. The serum ferritin was higher than 1500 μg/l (normal value: 20–250 μg/l). Roentgenogram of chest and urine analysis were normal as well as blood and urine cultures. Abdominal computed tomography showed hepatosplenomegaly. An electromyographic study was normal. Tests for antinuclear antibodies and rheumatoid factor were negative. Serum concentrations of immunoglobulins and complement were normal. Serological tests for hepatitis A, B or C, cytomegalovirus, parvovirus B19, human inmunodeficiency virus 1 and 2, Epstein-Barr virus, Mycoplasma, Treponema pallidum, Borrelia burgdorferi, Toxoplasma, Salmonella, Brucella, Legionella, Coxiella burnetti, Chlamydia and Rickettsia conorii were negative. The initial rubella IgG antibody titre was 140 000 IU/l.

During admission the patient looked acutely ill. Temperature rose to 40°C every evening with chills. The patient developed swelling and tenderness of proximal interphalangeal joints, elbows, wrists and knees. Roentgenograms of joints were normal. Because of cough a new chest roentgenogram was made. It showed a right basal lobe alveolar infiltrate that resolved spontaneously in 72 hours.

At this point, our patient fulfilled the criteria of Yamaguchi for adult onset Still's disease.[11] Initially, she was treated with acetylsalicylic acid 4 g/day by mouth, which had to be stopped because of an increase in liver enzymes, so prednisone 1 mg/kg/day orally was given with no improvement. Two weeks after admission methotrexate was added to diminish arthritis. The dose achieved was 7.5 mg by mouth weekly. The patient was discharged feeling well after staying in hospital for 34 days. At this moment rubella IgG antibody titre rose to 660 000 IU/l.

Our patient fulfilled Yamaguchi's criteria for adult onset Still's disease so this diagnosis was well established.[11 12] There was also strong evidence for acute rubella infection because the IgG antibody titre increased more than fourfold the initial one. It has been shown that children with primay rubella infection developing Still's disease increase both rubella IgG and IgM antibody titres.[13] In our case we think that rubella was more probably attributable to a reinfection than to a primary infection because the patient had been correctly vaccinated in childhood and this is also supported by the increase in IgG antibody titre without increase in IgM concentrations.[14] Moreover this seroconversion is not explained by a non-specific polyclonal stimulation after a generalised inflammatory disease because there was no increase in other measured antibody titres.

Although aetiology of adult onset Still's disease is unknown, some authors have tried to demonstrate that infective agents, especially viruses, can be the trigger of the illness in susceptible patients. In this way, echovirus 7,[1] mumps,[2] cytomegalovirus,[3–5] parainfluenza,[3] Epstein-Barr virus,[3–5] influenza A,[4] parvovirus B19,[6] hepatitis B or C[7 8] and rubella[1 3 9 10] have been associated.

The relation between rubella virus and adult onset Still's disease has been reported in some series and case reports[1 3 9 10] since the initial description by Bywaters in 1971.[15] Wouters *et al* performed exhaustive virological studies in five patients with adult onset Still's disease in an early phase of the illness and found evidence of viral infection in three cases, two of them corresponding to rubella.[1] The rubella virus genome has also been detected in peripheral blood cell population from patients with adult onset Still's disease.[16]

In summary, we think that the increased rubella IgG antibody titre in our patient should not be considered an anecdotal event and probably rubella virus has been the trigger of the illness. Our case, together with previously published reports,[1–10] supports the hypothesis about the role of viruses in the aetiopathogenesis of adult onset Still's disease.

FRANCISCO JAVIER ESCUDERO
ÓSCAR LEN
VICENÇ FALCÓ
TOMÁS FERNÁNDEZ DE SEVILLA
Service of Internal Medicine, Hospital General Universitario Vall d'Hebron, Barcelona, Spain

AGUSTÍ SELLAS
Service of Rheumatology, Hospital General Universitario Vall d'Hebron

Correspondence to: Dr Escudero, C/ Amapolas, 37 2ª Esc 1º 2ª, 08906 L'Hospitalet de Llobregat, Spain

1 Wouters JMGW, van der Veen J, van de Putte LBA, De Rooij DJRAM. Adult onset Still's disease and viral infections. Ann Rheum Dis 1988;47:764–7.
2 Gordon SC, Lauter CB. Mumps arthritis: unusual presentation as adult Still's disease. Ann Intern Med 1982;97:45–7.
3 Ohta A, Yamaguchi M, Tsunematsu T, Kasukawa R, Mizushima H, Kashiwagi H, *et al*. Adult Still's disease: A multicenter survey of Japanese patients. J Rheumatol 1990;17:1058–63.
4 Coffernils M, Soupart A, Pradier O, Feremans W, Nève P, Decaux G. Hyperferritinemia in adult onset Still's disease and the hemophagocytic syndrome. J Rheumatol 1992;19:1425–7.
5 Valtonen JMO, Kosunen TU, Karjalainen J, Valtonen M, Leirisalo-Repo M, Valtonen VV. Serological findings in patients with acute syndromes fulfilling the proposed criteria of adult onset Still's disease. Scand J Rheumatol 1997;26:342–5.
6 Pouchot J, Ouakil H, Debin ML, Vinceneux P. Adult Still's disease associated with acute human parvovirus B19 infection. Lancet 1993; 341:1280–1.
7 Lang DM, Petrozzi C. Immune complex disease-adult Still's disease? hepatitis B? West J Med 1985;143:680–1.
8 Castanet J, Lacour JP, Fuzibert JG, Perrin C, Rodot S, Ortonne JP. Adult Still's disease associated with hepatitis C virus infection. J Am Acad Dermatol 1994;31:807–8.
9 Huang SHK, De Coteau WE. Adult-onset Still's disease: an unusual presentation of rubella infection. Can Med Assoc J 1980;122: 1275–6.
10 Harth M, Thompson JM, Ralph ED. Adult-onset Still's disease. Can Med Assoc J 1979; 120:1507–10.
11 Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, *et al*. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19:424–30.
12 Masson C, Le Loët X, Lioté F, Dubost JJ, Boissier M-C, Perroux-Goumy L, *et al*. Comparative study of 6 types of criteria in adult Still's disease. J Rheumatol 1996;23:495–7.
13 Howard A, Ansell BM, Powell R. Immunoglobulin levels during rubella in children suffering from Still's disease. Ann Rheum Dis 1975;34:204.
14 Balfour Jr HH, Groth KE, Edelman CK. Rubella viraemia and antibody responses after rubella vaccination and reimmunisation. Lancet 1981;1:1078–80.
15 Bywaters EGL. Still's disease in the adult. Ann Rheum Dis 1971;30:121–33.
16 Newkirk MM, Lemmo A, Commenford K, Esdaile JM, Brandwein S. Aberrant cellular localization of rubella viral genome in patients with adult Still's disease-a pilot study. Autoimmunity 1993;16:39–43.

Raised plasma adrenomedullin in patients with systemic sclerosis complicated by pulmonary hypertension

Adrenomedullin is a hypotensive peptide newly found in human pheochromocytoma tissue.[1] The peptide comprises 52 amino acids with an intramolecular disulphide bond. The mRNA of adrenomedullin has been detected in normal adrenal medulla, heart, kidney, and lung. Adrenomedullin is produced in endothelial cells, vascular smooth muscle cells, and fibroblasts.[2] Adrenomedullin receptors are expressed in both vascular smooth muscle cells and vascular endothelial cells. Adrenomedullin has a vasorelaxant effect, antagonising the vasospastic effect of endothelin-1 and seems to be implicated in the physiological and pathological control of circulation. Through multiple biological effects in the circulatory system, adrenomedullin appears to reduce plasma volume and blood pressure, thereby protecting the cardiovascular system.[3] Furthermore, adrenomedullin regulates not only vascular tonus but also vascular function through the autocrine/paracrine system, stimulating cAMP formation in a dose dependent manner,[3] and exerting an anti-inflammatory effect by inhibiting the production of a chemoattractant from alveolar macrophages.[4]

Systemic sclerosis (SSc) is a chronic disease of unknown cause characterised by vascular changes and fibrosis of the skin and the visceral organs. Major complications of SSc are renal, myocardial, and pulmonary. Pulmonary hypertension (PH) is a common cause of death in patients with SSc. In the plasma of patients with PH the endothelin-1 level is raised.[5] In addition, it was recently reported that the adrenomedullin level is raised also in the plasma of patients with Raynaud's disease[6] or rheumatoid arthritis.[7] Therefore, we measured the concentrations of adrenomedullin and endothelin-1 in the plasma from patients with SSc, with or without PH, to elucidate the role of adrenomedullin in the pathogenesis of PH in SSc.

We obtained plasma from three women with SSc with PH (aged 43–72), 10 patients with SSc without PH (nine women, one man, aged 22–60), and one female patient with primary PH. The diagnosis of SSc was based on accepted criteria.[8] We diagnosed PH in