Concurrent onset of adult onset Still's disease and insulin dependent diabetes mellitus

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Abstract

Within two weeks after symptoms of an upper respiratory tract infection a 32 year old man developed Still's disease and insulin dependent diabetes mellitus, both of which have persisted for 24 months. Investigations failed to confirm acute infection but did show isolated persistent increase of serum antibodies to rubella virus. The simultaneous onset of these two diseases suggests a shared cause, possibly associated with rubella infection.

Adult onset Still's disease is an uncommon entity characterised by a multisystem illness with a wide constellation of features, notably fever, rash, and arthritis.¹ Its cause is unknown, though there are a few reports of association with viral illness.²⁻⁴ Insulin dependent diabetes mellitus is also thought in some cases to have a viral cause,⁵ but I am unaware of any reports of the simultaneous onset of these two diseases. Such a case is described here and the possible aetiological implications discussed.

Case report

A 32 year old man, who had previously been entirely well, presented with malaise and sore throat. In the preceding two weeks his wife and 2 year old child had had similar symptoms, which had resolved spontaneously. Despite oral antibiotics and diclofenac the patient's symptoms persisted and over the next four weeks he developed fever, chills, nocturnal sweats, myalgia, evanescent rash, polyuria, and a 12 kg weight loss, prompting referral to a rheumatologist.

Examination showed fever (39°C), faint erythematous truncal rash, splenomegaly, proximal limb soft tissue tenderness, and marked muscle wasting and weakness. There was no evidence of joint disease. Initial investigations showed a normochromic, normocytic anaemia (112 g/l), leucocytosis (16.2×10^9 cells/l), thrombocytosis (455×10^9 cells/l), an erythrocyte sedimentation rate of 120 mm/h, hyperglycaemia (22.1 mmol/l), and 4+ ketonuria. He was admitted to hospital and treatment started with synthetic human insulin, diclofenac, and paracetamol.

The following investigations in hospital were normal or negative: all cultures (six blood, two stool, two urine, one sputum): viral serology (including mumps, Coxsackie virus B1-6, cytomegalovirus, Epstein-Barr virus, and hepatitis A and B), antinuclear factor, rheumatoid factor, lupus erythematosus cells, anti-DNA, Venereal Disease Research Laboratory test, prothrombin

time, partial thromboplastin time, C3, C4, C1q binding, tri-iodothyronine, thyroxine, serum amylase, serum protein electrophoresis, and gallium scan.

Initial and convalescent serum rubella titres (haemagglutination inhibition) were both 1/640. Hepatic transaminases were five times normal. Abdominal ultrasound confirmed splenomegaly and showed decreased echogenicity of the pancreas. An abdominal computed tomography scan was normal except for hepatosplenomegaly. Percutaneous liver biopsy showed only minor focal portal tract inflammation. A two dimensional echocardiogram showed a small pericardial effusion. HLA typing results were A2,-;B44,51;Cw2,-;DR1,7.

The diagnosis of adult onset Still's disease was based on the typical clinical features, including the characteristic evanescent rash and daily fever in the absence of clinical or laboratory confirmation of other diagnostic possibilities.^{1 6} Despite diclofenac 150 mg/day and paracetamol 3250 mg/day he continued to have daily spiking fever up to 39.2°C. Initially, unexpectedly large amounts of insulin, up to 117 units daily, were necessary, but after two weeks' treatment the fever subsided and insulin requirements declined. He was eventually discharged from hospital asymptomatic but still requiring 22 units of insulin daily to control hyperglycaemia and ketosis.

One month later he developed monoarthritis of a knee, his first joint symptom. Viral and bacterial cultures of the synovial fluid were negative. Diclofenac was restarted but within two months he had profound persistent polyarthritis unresponsive to non-steroidal anti-inflammatory drugs, auranofin and methotrexate. Radiographs were initially normal but nine months later showed joint space narrowing of wrists, hips, knees, and ankles with sparing of fingers and toes. He now has ankylosis of the wrists. After 24 months of polyarthritis he remains rheumatoid factor negative and insulin requirements are unchanged at 22 units daily.

Discussion

This patient's illness fulfils recently proposed criteria for establishing the diagnosis of adult onset Still's disease.⁶ His illness started with a constellation of features typical of the disease— notably, evanescent rash and daily fever, and after two years of follow up no other diagnosis has evolved. Although a diagnosis of seronegative arthritis might be considered, the pattern of joint involvement and ankylosing of wrists is quite characteristic of Still's disease.^{7 8}

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Although it is possible that adult onset Still's disease and diabetes mellitus are unrelated in this patient, the concurrent onset of both diseases is striking and mere coincidence seems unlikely. Might one disease cause the other? I am unaware of any reports or proposed mechanisms of diabetes mellitus causing adult onset Still's disease. Conversely, it is possible that the hypermetabolic state associated with Still's disease might lead to secondary hyperglycaemia. This mechanism may well account for the unexpectedly high insulin requirements seen early in this patient's course but does not account for the diabetes mellitus itself because insulin is now still required to control ketosis and hyperglycaemia despite resolution of all symptoms of adult onset Still's disease other than the polyarthritis.

Thus in this patient adult onset Still's disease and insulin dependent diabetes mellitus may share a common cause. If so, then what factor(s) may be involved? Although little is known of the cause of either disease, the concept of host susceptibility genes has been proposed in both. This patient is HLA-D7 positive and an increased prevalence of this allele has been reported in Still's disease⁹ but not in insulin dependent diabetes mellitus. It has been suggested that the pathogenesis of adult onset Still's disease may entail immune complex vasculitis,¹⁰ but this mechanism would be unlikely to account for diabetes mellitus. Furthermore, neither immune complexes nor evidence of complement consumption was found.

Viral infection, though, has been associated with both adult onset Still's disease and insulin dependent diabetes mellitus and may have played a part in this patient. Preceding rubella infection has been reported in a few patients with Still's disease,²⁻⁴ and several viruses, particularly rubella, mumps, and Coxsackie B, have been incriminated in some cases of insulin dependent diabetes mellitus.⁵ The patient in this report, his wife, and 2 year old child all had had recent symptoms of an upper respiratory

tract infection. Acute viral infection could not be confirmed, but the titres of rubella antibody were four- to eightfold higher than those normally seen in our laboratory and this increase seems to be an isolated phenomenon rather than simply a non-specific response to inflammatory disease. In this case possibly the initial sample for viral serology, drawn approximately 40 days after the onset of symptoms, was obtained too late to detect an initial rise in antibody titres. Similar non-diagnostic increases of rubella antibody titres have been reported in Still's disease by others.¹¹

Thus in this patient with concurrent onset of Still's disease and insulin dependent diabetes mellitus the concept of a single agent, possibly viral, possibly rubella, inciting both diseases is tantalising. That specific aetiological agent, if it exists, remains to be confirmed, however.

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