Cold agglutinins and cryoglobulins in a patient with acute aortoarteritis (Takayasu's disease) and tuberculous lymphadenitis

Sir, Takayasu's disease is a granulomatous arteritis of unknown aetiology affecting the aorta, its major branches and the pulmonary artery [1, 2]. An association with tuberculosis has been described but not proven [2, 3]. We describe here a patient with Takayasu's disease and coexistent lymph node biopsy-proven tuberculosis in whom cold agglutinins and cryoglobulins were found during the acute phase of the illness.

A 22-yr-old female presented with a history of sudden onset of left-sided weakness. This was preceded by headaches, malaise, fatigue and myalgia lasting 2 days. Her blood pressure was 120/80 mmHg with all pulses palpable and no carotid bruits. She was afebrile. There was a palpable left supraclavicular lymph node. Chest and cardiac examinations were normal. Neurological examination confirmed a left motor sensory hemiparesis with a left homonymous hemianopia. A chest X-ray was normal. A computed tomography (CT) scan of the brain revealed a right middle cerebral artery infarct. Routine blood investigations revealed a haemoglobin of 11.7 g/dl with an erythrocyte sedimentation rate (ESR) of 57 mm/h. Four days after admission she had a fainting episode. Her blood pressure was found to be 90/75 mmHg with all pulses still present. A day later, clinical examination revealed bilaterally absent radial, brachial, subclavian and carotid pulses. Her neurological examination remained unchanged.

Investigations revealed an ESR of 70 mm/h. Atypical lymphocytes and rouleau formation were noted on the blood smear. All relevant blood tests were normal. The patient’s serum was tested for cold agglutinins and cryoglobulins. Agglutination at 4°C with cord cells, adult ‘O’ cells and the patient’s own cells revealed titres of 1/256, 1/4, 1/16, respectively. Anti-i antibodies were present at a titre of 1/256. Cryoglobulins were also detected. Schumm’s test and the Coombs test were negative. HIV serology, viral titres for hepatitis A, B and specifically C, mycoplasma, and infectious mononucleosis were normal or negative. A bone marrow examination revealed deficient iron stores but no lympho- or myeloproliferative disorder.

The cerebrospinal fluid was normal. An angiogram was performed and revealed the absence of the right and left subclavian and carotid arteries with a short ‘stump’ of the right brachiocephalic artery (Fig. 1). A carotid Doppler study demonstrated no flow through the common carotid, internal and external carotid arteries. Bilateral vertebral artery flow was evident.

The lymph node was biopsied and showed a large granuloma with central caseous necrosis. Epithelioid histiocytes and Langhans giant cells were present. Numerous other smaller caseating granulomata were present, some of which were coalescing. Acid fast bacilli were present. A diagnosis of tuberculous lymphadenitis was made.

The patient was treated conservatively with steroids and anti-tuberculous therapy. Ten weeks after the onset of pulselessness, her serum activities returned to normal. The cold agglutinins and cryoglobulins were no longer detectable. A follow-up angiogram was not performed.

The patient described herein fulfils the criteria for

Fig. 1. Digital subtraction angiogram of the aortic arch (left anterior oblique view) demonstrating dilatation of the aortic root and a short stump representing the brachiocephalic artery. There is no filling of the other major branches of the aorta.
diagnosis of Takayasu’s disease type B as proposed by Ishikawa [4]. The tuberculous lymphadenitis found in this patient is common in our population and therefore the argument of coexistence without causal relationship to Takayasu’s disease may hold true [5]. The occurrence of cold agglutinins and cryoglobulins during the acute phase of this patient’s illness, a hitherto undescribed finding, may be a factor(s) linking the two diseases.

Cold agglutinins are IgM complement-fixing autoantibodies that combine best with autologous red cell membrane antigens in the cold (0–4°C) causing agglutination [6]. They are present in low titres in normal serum and have no known function. Cryoglobulins, on the other hand, are immunoglobulins that undergo reversible precipitation in the cold [7]. In most instances, they occur as a mixture of IgG and IgM immunoglobulins. The simultaneous occurrence of cold agglutinins and cryoglobulins has been described to occur in chronic cold agglutinin disease, chronic lymphocytic leukaemia, and primary macroglobulinaemia [6, 7].

Neither cold agglutinins nor cryoglobulins alone or in combination have been described in tuberculosis or Takayasu’s disease. We excluded all the known causes of cryoglobulins and cold agglutinins in our patient, most notably hepatitis C and mycoplasma infection. Our patient also had no symptoms of a small vessel vasculitis. It is our proposal that the tuberculous infection in our patient resulted in the formation of cold agglutinins as well as cryoglobulins and that these either directly caused the aortoarteritis or contributed to the occlusion of the blood vessels. Cryoglobulins frequently circulate as immune complexes and cause small vessel vasculitis on the basis of deposition of antigen–antibody complexes with resultant vessel occlusion [7]. Large vessel vasculitis as seen in our patient has not been described with cryoglobulinaemia, but acute ischaemic stroke, as occurred in our patient, has been described in patients with mixed cryoglobulinaemia [8, 9].

An investigation into the role of cold agglutinins and cryoglobulins in the pathogenesis of Takayasu’s disease associated with tuberculosis is therefore necessary. This may be the ‘remote effect’ of tuberculosis alluded to by Lupi-Herrera et al. [1].

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