AN UNUSUAL CASE OF SERONEGATIVE WEGENER'S GRANULOMATOSIS: ACUTE PANCREATITIS AT ONSET, FOLLOWED BY ATRIO-VENTRICULAR BLOCK, NEUROLOGICAL AND KIDNEY INVOLVEMENT

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ABSTRACT

Wegener's granulomatosis WG) classically involves the upper respiratory tract, lungs and kidneys. Rarely, it also affects the gastrointestinal tract and heart. Symptomatic conduction defects in WG are quite uncommon and acute pancreatitis is rarely reported as the first presentation. This can result in diagnostic difficulty and may allow a potentially poor outcome.

We report a case in which WG started with gastrointestinal tract problems, was suspected after an heart and ear implication and diagnosed after a peripheral facial paresis with repeated negative ANCA test, and a fatal end by renal impairment after 3 months of starting immunosuppression therapy.

Key words: Wegener's granulomatosis, vasculitis, complete heart block, peripheral facial paresis

BACKGROUND

Wegener's granulomatosis WG) is an incurable form of multisystem necrotizing granulomatous vasculitis of unknown etiology. WG usually presents as a triad of airway necrotising granulomas, systemic vasculitis and focal necrotising glomerulonephritis. Initial signs are extremely variable, and diagnosis can be severely delayed due to the nonspecific nature of the symptoms. Rarely affected are the heart, the gastrointestinal tract and the central nervous system (1,2,3).

According to the American College of Rheumatology two or more positive criteria have a sensitivity of 88.2% and a specificity of 92.0% of describing WG: a) nasal or oral inflammation; b) lung lesions; c) kidney lesions; d) granulomatous inflammation within the arterial wall or in the perivascular area on biopsy (1,2).

CASE PRESENTATION

A 39-year-old woman without personal antecedents until the age of 35, when she developed a non-insulin dependent diabetes. After 2 years she became icteric with upper abdominal pain, associated with nausea and loss of appetite. Abdominal CT scan showed a pancreatic mass mimicking a tumor, but the histological result of the pancreatic biopsy showed chronic inflammation with no necrosis.

A year later she was admitted in our University Hospital in the coronary care unit in pre-syncope

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state, with mild fatigability, night sweats, gum pain, arthralgia and significant unintentional weight loss in the last 6 months 45 kg) and low fevers. She mentioned about a recent tick bite. A part from a 2/6 systolic heart murmur, she had strawberry gums, pale and clammy skin. Her initial electrocardiography showed a polymorphic ventricular tachycardia, first degree AV block evolving rapidly to Mobitz II second-degree AV block and then a complete heart block with narrow QRS and 40/min heart rate resistant to atropine. Permanent pacing was applied and exhaustive assessment was made which revealed slight anemia, leucocitosis, hipoalbuminemia with a discrete polyclonal hypergammaglobulinemia. Inflammation tests showed elevated C-reactive protein CRP), erythrocyte sedimentation rate ESR) and fibrinogen. Autoimmune tests, including p- and c-ANCA, chest X-ray and tumor markers showed negative results. The routine transthoracic echocardiography showed a concentric left ventricular and septal hypertrophy, with normal left ventricular ejection fraction with a thickened anterior mitral valve leaflet and mild mitral regurgitation, no pericardial effusion. Lyme antibodies were positive in the serum and this manifestation was interpreted as Lyme disease based on tick bite, cardiac findings, arthritis, positive Lyme serology and she was treated accordingly.

The next year, the patient was admitted in Neurosurgical Clinic showing a right peripheral facial paresis and rhinitis. The CT scan performed showed a right mastoiditis, reason for a surgical intervention. She was than addressed to our Neurology Clinic. Neurological examination showed a right peripheral facial paresis. Her laboratory data included a hemoglobin of 9.6 g/dL, leukocytosis of 13400 per mm^3. Her liver and renal function tests were normal. The inflammation tests showed an ESR of 100 mm per hour and fibrinogen of 672mg%. All autoimmune tests, were normal. Thorax CT scan showed ground glass infiltrates from alveolar hemorrhage. Histopathological result of the mastoid granulation tissue described a chronic inflammation with central necrotic granulomatous process with multinucleated giant cells and specific changes of vasculitis Fig. 1). Considered a WG with organ-threatening disease we started an immunosuppressive monthly pulse therapy with intravenous cyclophosphamide combined with methilprednisolon. Three months later she was hospitalized for her third cure of intravenous cyclophosphamide. At the time of patient presentation, on physical examination we found a saddle-nose deformity Fig. 2), an inflammation of nasal mucosa with multiple crusts, skin changes with raised dark spots due to bilateral vasculitis on the ankle and heel and her laboratory data showed an oligoanuric acute renal failure that was fatal in 3 days.

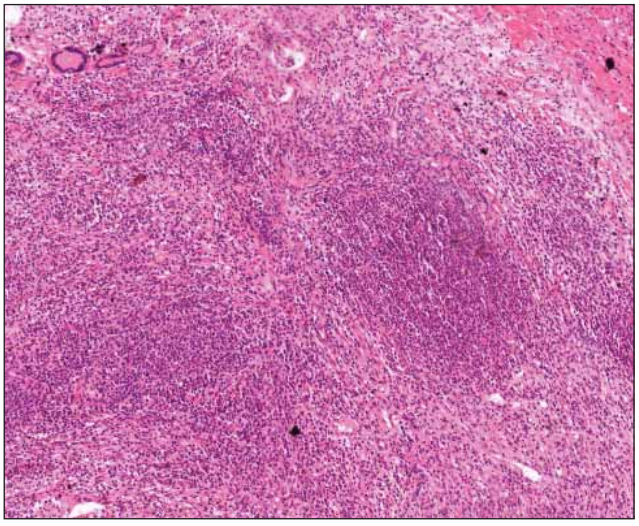

FIGURE 1. *The mastoid granulation tissue: chronic inflammation with central necrotic granulomatous process with multinucleated giant cells and histiocytic infiltrate hematoxylin and eosin x20)*

FIGURE 2. *Nasal bridge collapse saddle-nose deformity)*

DISCUSSIONS

Our case was a WG onset with acute pancreatitis followed by a heart conduction block.

Pancreatic association as an initial presentation of WG is limited to only a few reports and associated with a rapid progress to severe multiorgan involvement. This extremely rare initial presentation represents a challenge for the diagnostic process. (5-9).

Cardiac involvement is rarely documented antemortem. More rarely is described the involvement of myocard. Probable mechanisms for conduction abnormalities may include granulomas infiltrating the conduction system or atrio-ventricular nodal arteritis (10,11).

Neurological involvement is rarely inaugural. It commonly manifests as mononeuritis multiplex, peripheral or cranial neuropathy particularly cranial nerves II, VI and VII) or cerebral mass lesions and pachymeningitis (1,2,3). Our case like those described in the literature, developed neurological involvement facial palsy) later in the disease evolution. Cranial nerves are affected either by direct vasculitic injury, compression or extension of granulomatous disease (12). As in the series descrided by Nishino et al, neurologic involvement was shortly followed by kidney involvement. This simultaneity was found with a high frequency 83%) versus that in patients without neurological involvement, suggesting that peripheral neurological and renal involvement in WG are due to a similar mechanism, probably small-vessel vasculitis. Also, as in the mentioned study neurological complications occured later in the evolution of the disease, in the presence of other organ systems involved (12).

Our patient developed rather late WG-specific skin complications i.e. the so called „palpable purpura" in the form of small purple or red dots on the lower extremities, these being the most common skin rash in WG; a classic presentation of „strawberry gingival hyperplasia" was also seen (1, 2).

The involvement of nasal mucosa is the most common finding together with sinusitis. In our case this typical presentation appeared late in evolution. Our patient's had chronic mastoiditis, well described in the literature (1, 2, 13). Specific saddle nose deformity due to cartilage inflammation was present in our case in the advanced stage of WG together with severe fatal renal insufficiency (1,2).

A negative ANCA test, found in up to 20% of people with well-diagnosed WG, does not eliminate the possibility of WG in patients with characteristic clinical features. Though the ANCA test is useful, it cannot be used by itself either to diagnose WG or to reject it.

Therapeutic response to immunosuppressive agents combined with steroids is good, with remission rates of up to 90%. If treatment is initiated early, involvement of the lower respiratory tract and kidneys may be avoided (14). In a recent study researchers found that patients who had severe kidney disease, had an increased risk for treatment resistance (15-18).

Our patient started the appropriate treatment, but died due to severe renal complication; this form of WG is named *refractory* because it progresses and is unresponsive to glucocorticoids and cyclophosphamide. Early mortality and end-stage renal disease remain frequent outcomes for WG patients. In severe disease not responsive to this treatment, reviews are positive for: mycophenolate-mofetil, 15-deoxysperguanin, antithimocyteglobulin, rituximab and infliximab (1,2).

CONCLUSIONS

The patient presented initially an acute pancreatitis followed a symptomatic cardiac conduction defect with repeated negative ANCA test. This underlines the limitation of ANCA testing as well as the need for continuous thorough clinical evaluation, and the importance of organ biopsy in young patients.

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