

Anti-Golgi antibodies in adult Still's disease

Sirs,

Antinuclear antibodies (ANA) comprise a diverse group of antibody reactivities found mostly in systemic lupus erythematosus (SLE) and other connective tissue diseases (CTD) (1). Autoantibodies to cytoplasmic antigens are also of great interest since they may have diagnostic significance. For example anti-mitochondrial and anti-LKM antibodies are of special significance in the diagnosis of autoimmune liver diseases. Considering the case herein discussed, the polar granular pattern in interphase cells typical of anti-Golgi antibodies (2) is of our particular concern.

Anti-Golgi antibodies have been characterized by Western blot assays, immunoprecipitation (IP), and molecular cloning (2, 3). The pathological significance of these antibodies in patients with CTD is still unknown (3). In an earlier study, a group of investigators evaluated the Golgi antigens recognized by five autoimmune sera showing that these sera reacted with at least 14 components of molecular masses from 35 up to 260 kD (4).

The association of Golgi antibodies with Sjögren's syndrome (SS) dated back to the first report in 1982 (5). In 1992, a patient with SS was described to have an autoantibody specific for a 230-kD Golgi protein (6). In 1995, Fritzler *et al.* cloned and characterized golgin-245, target for antibodies in a patient with SS and glomerulonephritis (7). Subsequently, Erlich *et al.* described the nucleotide sequence from the previously reported 230-kD Golgi protein, which is essentially identical to golgin 245 (8). More recent work of Griffith *et al.* cloned a novel 97-kD Golgi complex autoantigen, golgin-97, associated with SS. Antibodies to golgin-97 were found in 20% of 60 sera known to have anti-Golgi antibodies; the majority of these positive sera were from patients with secondary SS (9).

Other than association with SS, Sohda *et al.* in 1994, cloned and sequenced a human 372-kD protein of the Golgi complex using the serum from a patient with RA (10). Later the same group also reported the cloning of a rat homologue of the 364-kD protein using the same serum (11). This protein is now known to be the same as giantin/macrogolgin described earlier in other studies (11,12). It appears obvious that anti-giantin antibodies are not associated with RA alone (13).

We herein describe the case of a patient with adult Still's disease in whom an anti-Golgi antibody was detected prior to treatment with methotrexate. The patient, a 63-year-old white male, first looked for rheu-

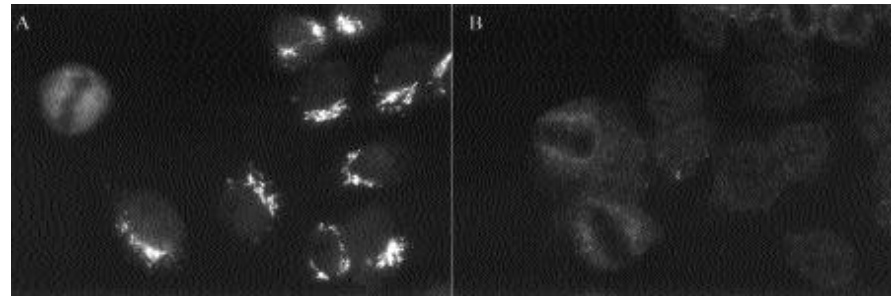


Fig. 1. Polar cytoplasmic pattern showing antibodies to the Golgi complex observed in indirect immunofluorescence using HEp-2 cells. Panel A, patient serum at 1:100 dilution at the initial diagnosis of Still's disease. Panel B, patient serum at 1:100 dilution 2 years after administration of methotrexate.

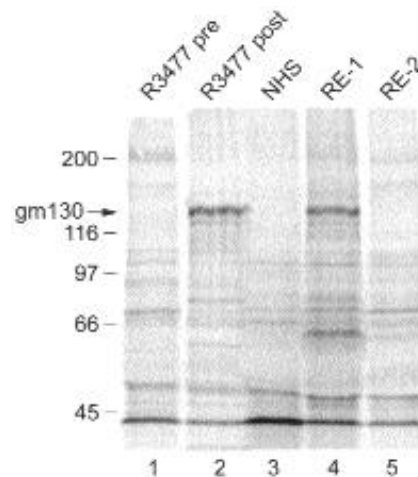


Fig. 2. Immunoprecipitation (IP) analysis of patient anti-Golgi antibodies at the diagnosis of Still's disease. HeLa cells were metabolically labeled with ^{35}S -methionine and grown in culture for 16 hours. Cell extracts were harvested by a lysis buffer containing 1% NP-40, 50mM Tris.HCl, pH 7.5, 150 mM NaCl, and mixed protease inhibitors. Soluble fractions were used as substrate for IP. Lane 1, pre-immune serum from rabbit R3477 as negative control; lane 2, rabbit anti-gm130 prototype antibody as positive control; lane 3, normal human serum control; lane 4, patient serum (RE-1) at the initial diagnosis of Still's disease; lane 5, serum of same patient (RE-2) 2 years after treatment.

matological help in May 1996. He had been presenting fever, evanescent rash on the trunk and swelling of wrists and metacarpophalangeal (MCP) joints for the last 6 months. Generalized myalgia and fatigue were also prominent. No sicca complex was present. A facial aspergyloma had been extirpated 2 years before. A previous history of pulmonary tuberculosis was also obtained.

Physical examination confirmed polyarthritides of MCP and wrists, as well as diffuse muscle tenderness. No lymphadenopathy was noticed. Cardiac, pulmonary and abdominal examinations were normal.

The chest X-ray showed residual changes of tuberculosis in upper regions of both lungs. Laboratory features included leukocytosis (20,900 cells, 80% of segmented neutrophils), erythrocyte sedimentation rate of 78 mm in the first hour (Westergren), and mild anemia. Renal and liver functions were preserved. Serum muscle enzymes were normal. Rheumatoid factor test was positive (80 units). Serological analysis for hepatitis B and C virus resulted negative. The ANA test using HEp-2 cells revealed a polar cytoplasmic pattern (1:80) compatible with the presence of anti-Golgi antibodies (Fig. 1). IP analysis using extracts from HeLa cells labeled with ^{35}S -methionine

confirmed that the patient's serum recognized a 130 kD protein corresponding to golgin-95/gm130 autoantigen (Fig. 2).

The diagnosis of adult Still's disease was established at that time. For the last 4 years, the patient has been on low-dose prednisone, oral methotrexate (7.5 mg weekly) and prophylactic isoniazid (200 mg daily). Clinical outcome can be considered as frankly favorable. Pulmonary or cardiac complications have not been noted so far. No fever, rashes or polyarthritides are present 3 years after diagnosis. The leukocyte count is 8400 cells and the ESR remains below 20 mm in the first hour. The ANA test is now negative, and anti-Golgi antibodies are not observed in immunofluorescence and IP assays (Fig. 1 and 2).

This is probably the first report of an anti-Golgi antibody in adult Still's disease. As previously reported, the majority of patients with anti-golgins have SS, SLE, or classic RA (14). In IP assay, the anti-Golgi seen in our patient recognized golgins-95/gm130; a similar antibody had been previously described in a patient with SLE and cerebellar ataxia, but not in other diseases (15). We cannot rule out the possibility that previous aspergyloma and tuberculosis have triggered the appearance of Still's disease and anti-Golgi antibody in this patient.

Letters to the Editor

Interestingly, the antibody has been cleared out of the circulation after induction of disease remission with methotrexate. Although the occurrence of any autoantibody in a single case is difficult to ascribe to a defined association, this report might bring about new similar associations.

The Golgi autoantigens look pleomorphic and complex (3). Nowadays, standardization of ANA techniques with HEp-2 cells supposedly facilitates the identification of anti-Golgi cytoplasmic patterns. Nevertheless, the refined specificities of anti-golgin antibodies by molecular methods, as well as clear-cut clinical associations, are yet to be set in patients with CTD.

H.L. STAUB E.K.L. CHAN
F. SOUZA C.A. VON MÜHLEN

Department of Rheumatology, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil; Department of Immunorheumatology, Lutheran University of Brazil, Canoas; Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California, USA.

Address correspondence to: Henrique Luiz Staub, Sao Lucas Hospital, Av. Ipiranga 6690, room 220, Porto Alegre 90610-000, Brazil.

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Drug-induced systemic lupus erythematosus associated with etanercept therapy in a child with juvenile idiopathic arthritis

Sirs,

Biological cytochrome inhibitors are considered to be an important recent therapeutic advance (1). Such inhibitors are utilized in several immune-mediated diseases that are not responsive to conventional treatments. In particular, biological agents such as anti-tumor necrosis factor alpha (TNF- α) has proved to be effective and safe both in rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA). Nevertheless, evidence of their potential toxicity needs to be considered and evaluated (2). Recently, Shakoob *et al.* (3) report 4 cases of a syndrome resembling systemic lupus erythematosus (SLE) induced by etanercept. All of these patients were adult females suffering from refractory RA. Symptoms resolved spontaneously in all patients 2-6 weeks after etanercept withdrawal. The autoantibody status (ANA and anti-dsDNA) before the onset of the syndrome was not reported for any of these patients.

At our tertiary referral center for rheumatic disease 13 paediatric patients with JIA have

been treated with etanercept. One of these, a 12-year old boy with a 10-year history of polyarticular JIA, developed a drug-induced syndrome resembling SLE. After the failure of all conventional treatments for JIA, he had started treatment with etanercept at a dosage of 25 mg twice week. He was ANA positive (1:80-1:160) and negative for anti-dsDNA before etanercept was started. ANA and anti-dsDNA measurements were carried out using an indirect immunofluorescence method on Hep-2 cells; the cut-off for positivity in our laboratory is 1:80 for ANA and 1:40 for anti-dsDNA. The boy was seen monthly for clinical and laboratory follow-up including autoantibody measurements.

During treatment his ANA titre progressively rose to 1:2560, while C3 and C4 remained within the normal range. Seventeen months after starting the drug, the child developed daily fever peaks, urticaria involving the face and abdomen, and swelling of the hands. Anti-dsDNA antibody levels were found to be significantly elevated (1:320). Etanercept was stopped but the symptoms cleared only after corticosteroid treatment (1mg/kg/day) was started. After a few weeks ANA had decreased to 1:320 and anti-dsDNA disappeared. Steroid therapy was tapered and stopped after 2 months.

To our knowledge only 6 cases of SLE-like syndrome have been described in adult patients receiving etanercept (4). ANA and anti-dsDNA increases have been reported in 11% and 15% respectively of the cases treated. Our case represents the first paediatric patient with an SLE-like syndrome attributable to etanercept. Although ANA positivity is not specific for SLE, a progressive rise in ANA to very high titres, as occurred in our patient, might be considered an early sign of drug-induced SLE.

We suggest that ANA and antiDNA should be evaluated in all patients before starting therapy with etanercept and then monitored during treatment. A progressive increase in the ANA and/or anti-dsDNA titre may be predictive of the risk of developing an SLE-like syndrome due to TNF- α inhibitors and in these cases the suspension of etanercept treatment should be considered. Studies to gather reliable follow-up data in paediatric patients are warranted to define the type and incidence of adverse reactions related to etanercept and to identify the indications for its suspension (5).

L. LEPORE, MD* V. LEONE, MD
F. MARCHETTI, MD A. VENTURA, MD
S. FACCHINI, MD

Clinica Pediatrica, IRCCS Burlo Garofolo, Università di Trieste, Via dell'Istria 65/1, 34137 Trieste