Letters to the Editor

Mesalazine-induced Churg-Strauss syndrome in a patient with Crohn's disease and sclerosing cholangitis

Sirs,
Churg-Strauss syndrome (CSS) is a rare disorder characterized by asthma, eosinophilia and systemic vasculitis (1). Three different phases can usually be recognized in CSS: asthma and atopic allergies such as rhinitis may precede of months, and sometimes of several years, the development of an eosinophilic infiltrative disease with eosinophilic pneumonia or gastro-enteritis followed by the vasculitic phase (1). The etiology of CSS is unknown but putative triggering factors have been identified, including desensitization, vaccination, rapid discontinuation of oral corticosteroid and, more recently, some drugs such as macrolide antibiotics and leukotriene receptor antagonists (2, 3).
We report a case of Churg-Strauss syndrome in a patient with Crohn's disease associated with use of mesalazine, a compound known to induce rarely eosinophilic pneumonia (4).
A 39-year-old man with a 10-year history of atopic rhinitis, nasal polyposis, and asthma presented with weakness, fever, weight loss, arthralgias, vertigo, and paresthesias. He was on salbutamol, mesalazine and ursodeoxycholic acid. Mesalazine had been started 10 months before presentation for Crohn's disease and sclerosing cholangitis, both histologically proven.
At presentation, his eosinophil count was 12,124 x mm^3 (56% of total), erythrocyte sedimentation rate 41 and C-reactive protein 7 mg/L (nv < 5). A urine specimen revealed haematuria (1 plus).
Antineutrophil cytoplasmic antibody (ANCA), antinuclear antibodies (ANA), and rheumatoid factor were negative. A nuclear magnetic resonance of the skull revealed pansinusitis, whereas a computed tomography of the lung showed initial centrolobular emphysema. Pulmonary function tests disclosed a mild obstructive disease. Electromyography of peripheral nerves was indicative of mononeuritis multiplex. A bone-marrow biopsy specimen showed extensive eosinophilic infiltration. Since a stool specimen was positive for Blastocystis hominis, the patient was discarded with metronidazole treatment.
One month later, the patient was admitted again because of worsening of vertigo. Laboratory tests confirmed the presence of eosinophilia (46.4%), and increased inflammatory markers.
An ENT doctor examination revealed vestibular decompensation and right perceptive hypacusia. Subsequently, there was the occurrence of spontaneous nystagmus and a left third cranial nerve palsy. A repeat nuclear magnetic resonance of the skull showed new multiple small ischemic lesions.
Because of the presence of asthma, marked eosinophilia, sinusitis, and neuropathy a diagnosis of Churg-Strauss syndrome was made and treatment with prednisone 1 mg/-Kg was started with prompt clinical improvement, normalization of inflammatory indices and of eosinophilia.
Since no reports on the association of Churg-Strauss syndrome with Crohn's disease were found in a literature search, and based on the well-known recognition that drugs can act as triggering factors in Churg-Strauss vasculitis (2, 3), mesalazine was stopped.
Eight months after diagnosis the patient is well under treatment with prednisone 15 mg/day. His eosinophil count is normal as well as his erythrocyte sedimentation rate and C reactive protein.
The cause(s) of Churg-Strauss syndrome is usually not known, but among putative triggering factors vaccinations, desensitisation, antibiotics and, more recently, leukotriene receptor antagonists have been described (2-3, 5). Mesalazine is known to induce eosinophilic pneumonia and can cause activation of eosinophil (4, 6). More rarely, it has been associated with vasculitis-like syndromes and, in a single case, with Churg-Strauss syndrome in a patient with ulcerative colitis (4, 6-10). In most cases blood eosinophilia was present (6-8).
To our knowledge this is the first report of a case of Churg-Strauss syndrome in a patient with Crohn's disease and sclerosing cholangitis. Even though we could not demonstrate a cause-effect relationship between mesalazine and Churg-Strauss syndrome, we believe that our patient's illness was probably caused by this drug because of its capacity to induce eosinophil activation and hypersensitivity reactions.
We suggest that mesalazine should be used with caution in patient with asthma.

R. A. SINICO
E. SABADINI
A. M. MARESCA[1]

Unità Operativa Semplice di Immunologia Clinica, Dipartimento Area Medica e Dipartimento di Nefrologia e Immunologia, Azienda Ospedaliera Ospedale San Carlo Borromeo, Milano, and [1]Dipartimento di Medicina Interna, Università dell'Insubria, Ospedale di Circolo, Fondazione Macchi, Varese, Italy.

Address correspondence to: Dr. R. A. Sinico, U.O.S. di Immunologia Clinica, Azienda Ospedaliera Ospedale San Carlo Borromeo, Via Pio Secondo 3, 20153 Milano, Italy.
E-mail: renato.sinico@oscb.sined.net

References

1. NOTH I, STREK ME, LEFF AR: Churg-Strauss syndrome. *Lancet* 2003; 361: 587-94.
2. EUSTACE JA, NADASDY T, CHOI M: The Churg-Strauss syndrome. *J Am Soc Nephrol* 1999; 10: 2048-55.
3. GUILLEVIN L, COHEN P, GAYRAUD M *et al.*: Churg-Strauss syndrome. Clinical study and long-term follow up of 96 patients. *Medicine* 1999; 78: 26-37.
4. TANIGAWA K, SUGIYAMA K, MATSUYAMA H *et al.*: Mesalazine-induced eosinophilic pneumonia. *Respiration* 1999; 66: 69-72.
5. HELLMICH B, EHLERS S, CSERNOCK E, GROSS WL: Update on the pathogenesis of Churg-Strauss syndrome. *Clin Exp Rheumatol* 2003; 21 (S 32): S69-77.
6. MORICE AH, KUMWENDA J, QURESHI N, CURRAN A: Mesalazine activation of eosinophil. *Lancet* 1997; 350: 1105.
7. HONEYBOURNE D: Mesalazine toxicity. *Br Med J* 1994; 304: 533.
8. WAANDERS H, THOMPSON J: Kawasaki-like syndrome after treatment with mesalazine *Am J Gastroenterol* 1991; 86: 219-221.
9. DENT MT, GANAPATHY S, HOLDSWORTH CD, CHANNER KC: Mesalazine induced lupus-like syndrome. *Br Med J* 1992; 305: 159.
10. LIM AG, HINE KR: Fever, vasculitic rash, arthritis, pericarditis, and pericardial effusion after mesalazine. *Br Med J* 1994; 308: 113.

A case report of Takayasu arteritis with history of retroperitoneal fibrosis and coeliac disease: An unusual association

Sirs,
Takayasu arteritis (TA) is an idiopathic, inflammatory granulomatous vasculopathy of the aorta and its main branches. The pulmonary arteries can also be involved. The inflammation is caused by infiltration of lymphocytes and occasional giant cells in three vessel layers which leads to wall thickening and fibrosis with destruction of elastic tissue in the large vessel (1).
A retrospectively review of medical records of 36 patients with TA has shown an association with other inflammatory autoimmune diseases such as, rheumatoid arthritis, systemic lupus erythematosus, spondyloarthropathy, Crohn's disease, ulcerative colitis, coeliac disease and chronic thyroiditis (2).
We described an unusual association of TA in a young women with a medical history of coeliac disease and idiopathic retroperitoneal fibrosis .
In May 2005 a 34 year-old woman was admitted to the Vascular Surgical Unit of our Hospital with sub-nail necrotic lesions on her right hand. The patient reported episodes of claudicatio intermittens in the last six months, fatigue and discomfort in the muscles of her upper right arm, after minor efforts.
Remote anamnesis showed recurrent episodes of mono-oligoarthritis of knee and ankles since the age of six.
In 2000 as a result of persistent episodes of diarrhoea, progressive weight loss and iron deficiency anemia she was admitted to the Internal Medicine Unit where positivity of Antigliadin antibodies IgA, Antiendomysial antibodies IgA and Anti-Tissue transglutaminase IgA was demonstrated. A jejunal

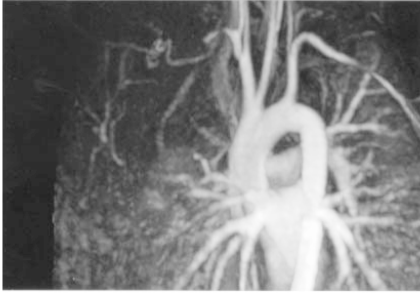

Fig. 1.

biopsy showed absence or reduced height of villi, increased crypt cell proliferation and increased lymphocytes and plasma cells in the lamina propria. A seronegative arthtritis in coeliac sprue was diagnosed and therefore the patient started a gluten free diet with a good serological and clinical response.

In 2003 due to persistent episodes of low back pain followed by pain in the left flank, the patient was admitted to the Urology Unit where an echography showed bilateral hydroureternephrosis with acute renal failure. A pig-tail stent was introduced. After one week, an abdomen CT showed bilateral ureteral stenosis with hydronephrosis and the patient underwent surgical ureterolysis with asportation of the adherential tissue. The hystological findings confirmed the diagnosis of an idiopathic retroperitoneal fibrosis without secondary diseases.

During the period in our hospital in May 2005 the objective examinations showed absence of pulse in the right radial artery. Blood examinations showed : ESR 17 mm/h, CRP 0.88 mg/dl, negative Lupus Anti coagulant, Anti-cardiolipin, Antiβ2 glycoprotein I, ANA and ANCA antibodies. Study of cytokine serum levels showed normal range level of TNF-α but high serum level of IL-6 (4.16 pg/ml) and IL-8 (50 pg/ml). Study of circulating mononuclear cells showed a reduction of lymphocytes CD8 (244 cells/mcl), CD19 (125 cells/mcl), and CD56 (71 cells/mcl) but CD4 were in the normal range.

Angio-Magnetic Resonance and Aortography, that is the gold-standard for definitive diagnosis of TA, showed an obstruction of the subclavian artery 20 mm after the origin of the vertebral artery, with collateral circulation in the internal thoracic artery and rehabilitation of the brachial artery (Fig 1). ^{18}F-FDG positron emission tomography showed an uptake in the right internal carotid artery and in the abdomen.

We also carried out a study of identification of Human Histocompatibility Complex with PCR(Polymerase Chain Reaction)-SSO using sequential specific oligonucleotide probes. The patient showed the following aplotypes : A11 A23, B08 B44, C04 C07, DRB1*03 DRB1*07, DQB1*0202, DQB1*0201, DQA1*0201, DQA1*0501.

The patient fullfilled ACR criteria for Takayasu arteritis (3) and was referred to the Vasculitis Center where she started therapy with methylprednisolone 16 mg/day and low molecular weight heparin.

To the best of our knowledge, this case report is the first showing an association between TA, idiopathic retroperitoneal fibrosis (IRF) and coeliac disease (CD). All three diseases have an autoimmune pathogenesis. An association between TA and coeliac disease was reported in literature in two case reports which showed an improvement in coeliac activity but with progressive renal vascular hypertension treated by angioplasty with stent implantation (4-5). Also an association between TA and idiopathic retroperitoneal fibrosis was described in two case reports (6-7) but recent advances showed morphological findings which would justify the separation between the two diseases. Idiopathic retroperitoneal fibrosis is a systemic disorder under the general heading of Chronic Periaortitis (CP). The clinical history, angiography non-MRI and ^{18}F-FDG positron emission tomography have allowed a definite diagnosis, leading to an understanding of the disease activity in our patient.

^{18}F-FDG positron emission tomography show in patients with CP the presence of large-vessel vasculitis involving abdominal aorta and common iliac arteries and the vascular uptake in large thoracic arteries was seen in 43% of patients (8).

With regards to the immunological study, the profile of our patient's citokines showed normal serum levels of TNF-α but IL-6 and IL-8 levels out of normal range with normal levels of ESR and CRP. Some studies have found that ESR and CRP are not able to differentiate patients with clinically active and inactive TA while IL-6 and IL-8 could be promizing markers of disease activity (9). Moreover IL-8 shows a normalization in most follow-up patients after immunosuppressive therapy (10).

The study of the subsets of lymphocytes population by flow cytometric analysis in our patient showed a reduction of CD8, CD19, CD16/56. However these findings, such as autoantibody production, do not appear in many other papers and is still under dispute. It will be interesting to have more reports on these data in order to achieve correct interpretation (11).

The study of the genes of of major histocompatibility complex showed important data about a possible link between the diseases. Our patient showed a double association with alleles for coeliac disease DQB1*0202, DQB1*0201, DQA1*0501 linked to DRB1*03 DRB1*07, but DRB1*07, DQB1*0202 also showed an association with Takayasu arteritis in a report on Korean patients (12). No other typical association with other alleles of TA, which had been shown in a large series of patients, or with alleles of IRF was detected in our patient.

This is the first case report of TA in association with both IRF and CD, but our study failed to find a genetic link between the three diseases.

M. BENUCCI[1]
M. MANFREDI[2]
S. MICHELAGNOLI[3]
A. BERTELLI[4]
F. CANTINI[5]

[1]Section of Rheumatology; [2]Section of Immunology and Allergology; [3]Angiology Unit, Nuovo Ospedale S.Giovanni di Dio, Florence; [4]Section of Immunohaematology Ospedale SS. Annunziata Florence; [5]Internal Medicine Unit and Section of Rheumatology Referral Vasculitis Center Ospedale Misericordia e Dolce, Prato.

Address correspondence to: Maurizio Benucci, MD; Rheumatology Unit ASL 10, Nuovo Ospedale S. Giovanni di Dio, via di Torregalli 3, 50143 Firenze, Italy.
E-mail: maubenucci@tiscali.it

References

1. JOHNSTON SL, LOCK RJ, GOMPLESS MM: Takayasu's arteritis (review). *J Clin Pathol* 2002; 55: 481-6.
2. OKTA Y, OKYA Y, FUJII K, TSUCHIHASHI T, SATO K, ABE I: Inflammatory disease associated with Takayasu's arteritis. *Angiology* 2003; 54: 339-44.
3. AREND WP, MICHEL BA, BLOCH DA: The American College of Rheumatology 1990 Criteria for the classification of Takayasu's artheritis. *Arthritis Rheum* 1990; 33: 1129-32.
4. KORINEK J, LUBANDA JC, KARETOVA D *et al.*: Takayasu's disease associated with autoimmune thyroiditis and coeliac disease. Clinical course and limitation of treatment. *J Mal Vasc* 2001; 26: 191-5.
5. STADLMAIER E, SPRAY A, TILLICH M, PILGER E: Midaortic syndrome and coeliac disease: a case of local vasculitis. *Clin Rheumatol* 2004; 7 Epub ahead of print.
6. FAJAC A, GALEZOWSKI N, CORMIER JM, DUCLOS FM, HERREMAN G: Inflammatory arteritis of Takayasu's disease type and retroperitoneal fibrosis. *Rev Med Interne* 1988; 9: 436-7.
7. HOUMAN H, HAOUET S, LAMLOUM M, GHORBEL IB, MILED M: Retroperitoneal fibrosis associated with Takayasu's arteritis. *Ann Med Interne* 1998; 149: 107-8.
8. SALVARANI C, PIPITONE N, VERSARI A *et al.*: Positron emission tomography (PET): evaluation of chronic periaortitis. *Arthritis Rheum* 2005; 53: 298-303.
9. SALVARANI C, CANTINI F, BOIARDI L, HUNDER GG: Laboratory investigation useful in giant arteritis d Takayasu's arteritis *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): S23.
10. TRIPATHY NK, SINHA N, NOTYANAND S: Interleukin-8 in Takayasu's arteritis: plasma levels and relationship with disease activity. *Clin Exp Rheumatol* 2004; 22 (Suppl. 36): S27.
11. UPPAL SS, VERMA S: Analysis of clinical profile, autoimmune phenomena and T cell subset (CD4 and CD8) in Takayasu's arteritis: A hospital based study. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): S112.
12. PARK MH, PARK YB: HLA typing of Takayasu's arteritis in *Korea. Heart Vessels* 1992; (Suppl. 7): S68-72. PMID: 1360975.

Acknowledgements

A special thanks to Miss Patricia Manfredi for her precious help in the English revision.