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Churg-Strauss Syndrome: a diagnosis not to be forgotten

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SUMMARY

Churg-Strauss syndrome (CSS) is a peculiar form of vasculitis with involvement of small- and medium-size arteries, histologically characterized by necrotizing granulomas in vessel walls and in perivascular tissues. The Authors report a case of CSS occurred in a young man being treated with corticosteroids for a diagnosis of asthma. The patient was hospitalized because of fever, diarrhoea and abdominal pain; the first assessment showed leucocytosis and eosinophilia,increase in flogosis indexes and anti-pANCA antibodies positive.

A few days later an acute peritonitis with multiple intestinal perforations occurred and a partial resection of small bowel was performed,followed by another resection of an ileal segment because of a new double perforation close to the previous intestinal anastomosis. In the bowel resection pieces necrotizing vasculitis and granulomatous infiltrates involving lymphocytes and eosino- phils were observed. Although the severe intestinal involvement and especially the symptoms necessitating iterative surgery were significant factors of poor prognosis the patient was successfully treated firstly with metylprednisolone only and then with monthly administration of immunosuppressive drugs combined with lower daily dose of steroids. The CSS diagnosis is not to be forgotten althoughits early clinical features can be frequently mistaken for an allergic disease; an early diagnosis can allow to perform the best treatment, to reach the disease remission and to improve the quality of life of the patients.

KEY WORDS: Churg-Strauss vasculitis steroids

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INTRODUCTION

Dates back to 1951 and was first reported by the US anatomopathologists Jacob Churg and Lotte Strauss the description of a peculiar form of vasculitis with prominent involvement of small - and medium-sized arteries, histologically characterized by the formation of predominantly eosinophilic and necrotizing granulomas in vessel walls and in perivascular tissue (Churg and Straus, 1951; Guillevin *et al.,* 1996).

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Clinical onset of the 13 cases reported by Churg and Strauss presented with severe asthma, fever and hypereosinophilia, which led almost invariably to a lethal outcome within a period ranging from a few months to nearly ten years.

Based on the observations of Churg-Strauss, this new pathological entity - which was named after its discoverers - was classified as a malignant form of allergic granulomatosis and systemic angiitis, characterized by a more rapid progression as well as by a poorer prognosis compared with similar disease entities known till then.

The Churg-Strauss syndrome (CSS) is a disorder whose incidence has not yet been estimated, mostly affecting caucasian males aged between 20 and 50 (Guillevin *et al.,* 1991).

CSS generally develops as new onset and progressively severe asthma or other allergic forms,

sometimes triggered by inhaled allergens. (Orriols *et al.,* 1996; Yousem and Lombard, 1998). After a few years, this picture progresses to peripheral eosinophilia and to the formation of eosinophilic infiltrates involving the respiratory and digestive tract, which cause recurrent pneumonia, pleuritis and gastroenteritis. The final step is the development of frank systemic vasculitis running with fever, myoarthralgias and hypertension, often leading to irreversible cardiomyopathy (Kinoshita *et al.,* 1999; Gross *et al.,* 2000); in the advanced phases of the disease peripheral neurophaties as well as skin affections can be observed.

Diagnostic suspicion, suggested by peripheral eosinophilia values up to >80% and by a marked increase in serum IgE, is also confirmed by the detection of circulating autoantibodies directed against neutrophil cytoplasmatic proteins (anticytoplasmic neutrophil antibodies ANCA), which seem to have a relevant role in the pathogenesis of vascular lesions, above all of those developing in the glomerular region and in the Central and Peripheral Nervous System; in CSS the rate of these antibodies varies from 39% to 59% and is lower compared to other systemic disorders such as Wegener's granulomatosis or microscopic polyangitis (Sablé-Fourtassou *et al.,* 2005; Frohnert and Sheps, 1967).

Before the introduction of steroid therapy, the prognosis "quoad vitam" was unfavourable in more than 80% of cases within the first 5 years after diagnosis (Leib *et al.,* 1979; Luqmani *et al.,* 1994).

Although the therapeutic approach with steroids and cytotossic drugs (in particular cyclophosphamide) has lead to a consistent improvement in survival (at the moment estimated to reach about 82% within 5 years after diagnosis) and quality of life, CSS prognosis remains unfavourable in all clinical cases presenting with one or more of the following factors (all together constituting the prognostic index called Five Factor Score, FFS): renal failure, proteinuria >1 g/die, clinical signs of gastrointestinal and/or Central Nervous System involvement, cardiomyophaties.

At this regard, during a recent survey in more than 300 cases of systemic vasculitis, the development of renal impairment and the appearance of gastrointestinal symptoms significantly correlated with a higher mortality index (Guillevin *et al.,* 1996).

Of prognostic value complementary to FFS is the Birmingham Vasculitis Activity Score (BVAS), which allows a dynamic assessment of the disease by discriminating between tissue damages due to previous stages of vascular flogosis and injuries imputable to disease activity (Cruz *et al.,* 2003; de Groot *et al.,* 1996).

In a broad percentage of cases, the use of metylprednisolone and cyclophosphamide can induce and maintain symptom remission; after the first 3-6-months of therapy, cyclophosphamide can be replaced with azathioprine (gradually tapering the dosage of both initial agents according to symptom evolution) or with methotrexate (Watts *et al.,* 2000).

In the most severe forms, expecially those characterized by necrotizing glomerulonephritis, the method of «plasma exchange», in association with steroid and cytotossic therapy, can promote the recovery of renal function (Jayne and Lockwood, 1993); refractory cases were also treated with e.v. immunoglobulins in association with immunosuppressive drugs, resulting in satisfactory middle-term outcomes (Churg *et al.,* 1995).

Here we report a case of CSS and describe its rapidly progressing course, its diagnostic iter as well as the implementation of a therapeutic management structured in both medical and surgical interventions.

CASE DESCRIPTION

L.M., a 43-year-old man, came to our observation in October 2005, complaining of fever, abdominal pain and diarrhoea, initially ascribed by the patient himself to the frequent consumption of raw equine meat.

Remote pathological anamnesis highlighted the presence of bronchial asthma, developed about one year before and treated with β2-agonists and inhaled steroids, as well as of a form of iatrogenic epilepsy developed at the age of 35 after surgical resection of a cavernous hemangioma in the right frontal lobe and treated from then on with barbiturates.

The first assessments showed leucocytosis (32.000/mm^3) with eosinophilia (65%), a marked increase in flogosis indexes (ESR 74 mm at the

first hour; CPR 29 mg/dl) and rheumatoid factor (94 UI/ml) and anti-pANCA antibodies positive (1:160 in indirect immunofluorescence); coproculture and coproparassitological tests were negative, as well as Mantoux intradermoreaction.
In October, 25th, the patient underwent abdominal CT, which showed an extensive modification of vascularity in the hepatic segments II,V,VI, III, IV and in the spleen, accompanied by an inflammatory reaction of lymphonodes; during abdominal ecography, which was performed some days later, a bioptic specimen was obtained from a nodular formation detected in the hepatic segment II. Histological examination revealed the presence of active necrotizing vasculitis in the intratubular veins and arteries, as well as of flogistic infiltrates with a high percentage of eosinophils in portal spaces (Figure 1).
CT encephalic images (obtained the 28th October) revealed, beyond the surgical outcomes in right frontal position, diffuse inflammation of maxillary and frontal sinuses.
Some days after hospital admission, due to a sudden exacerbation of abdominal pain, the patient underwent a surgical visit and a laparotomic emergency intervention, during which, after the detection of a generalized peritonitis with diffuse ischemic involvement of small bowel (which was found to be also site of multiple perforations), ascending colon and cecum, a partial intestinal resection with jejunal-ileal anastomosis was performed.
Based on histological examination of resected tissues, which suggested the presence of necrotizing-ischemic vasculitis with inflammatory granulomatous infiltrates of limphocytes, polymorphonuclear cells and eosinophils, the diagnosis of p-ANCA-associated vasculitis with high disease activity indexes was established: Birmingham Vasculitis Activity Score (BVAS) 15; Five Factor Score (FFS) 1 (Figure 2a, b, c).
Steroid therapy with metylprednisolone 20 mg bid was then instituted.
During the post-operative course the patient had a urinary tract infection (UTI) by *Proteus mirabilis*, treated with antibiotic therapy (500 mg meropenem tid/die for 10 days).
During the hospitalization in the Department of Hepato-Pancreatic Surgery, where the patient had been moved to in the meanwhile, a further laparoscopic examination (15th November) indicated a double intestinal perforation proximally off the anastomosis previously performed, with loops of oedematous aspect up to the first jejunal tract and multiple intraperitoneal purulent harvests. The resection of an ileal segment of about 60 cm was then performed. Histological examination of the surgical specimen confirmed the finding of necrotizing vasculitis with granulomatous infiltrates in which the eosinophilic component was significantly represented.

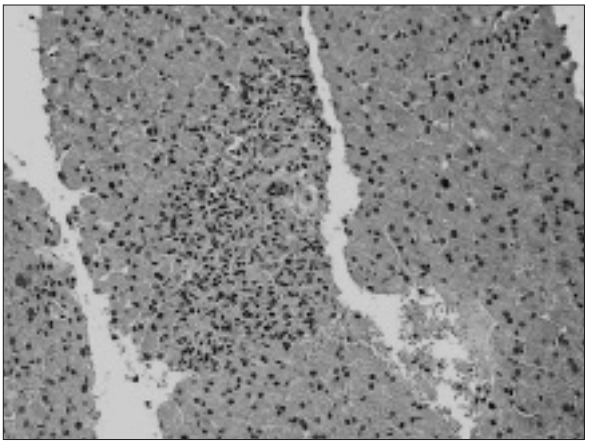

FIGURE 1

Since clinical, immunological and histological data concerning this case indicated for certain the diagnosis of CSS, some weeks after the last intervention the patient was transferred to the Operative Unit (OU) of Rheumatology, in order to work out the most effective therapeutic strategy: in view of the particularly aggressive course of the disease and of the severe involvement of gastrointestinal tract, it was deemed appropriate to administer steroids (metylprednisolone 16+8 mg/die) in association with cyclophosphamide, initially per os (mg/kg/die) and then intravenously (a 500 mg bolus diluted in 500 ml of 5% glucose solution every two weeks).
Over the first 6 months of therapy, during which 10 boluses of cyclophosphamide were administered, episodes of recurrent UTI caused by *P. mirabilis* and by *Providencia rustifiani* occurred; however, at the end of this first treatment period, a significant improvement in the disease activity indexes was observed: BVAS fell to 11 and FFS fell to 0.
We decided to continue immunosuppressive therapy administering further 6 boluses of cyclophosphamide (1 g every 30 days from July to

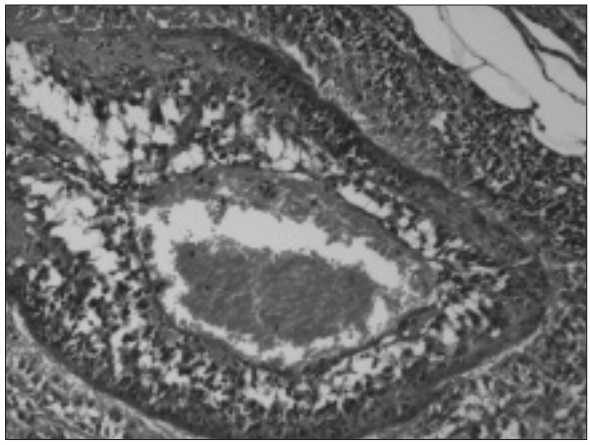

FIGURE 2a

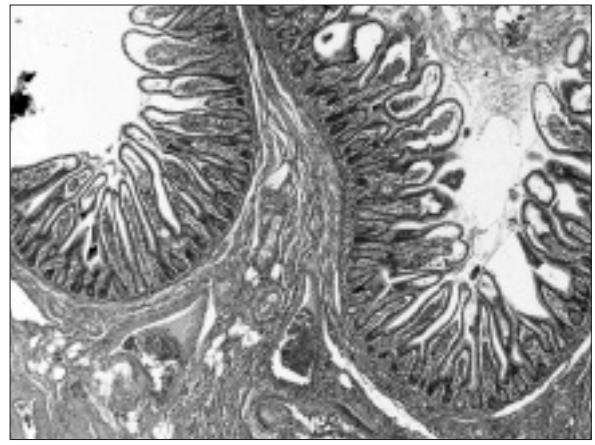

FIGURE 2b

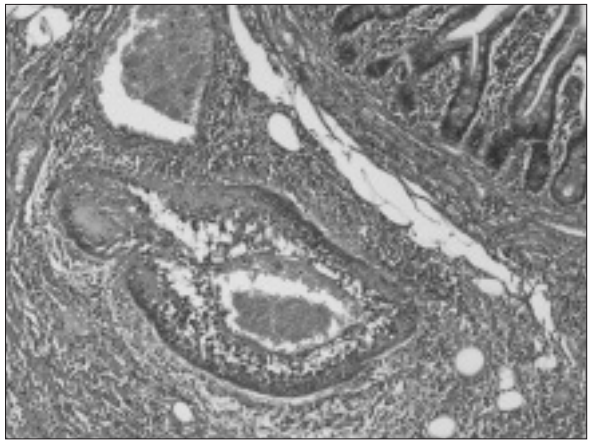

FIGURE 2c

December 2006), tapering in the meantime metylprednisolone posology to 8+4 mg/die.
An the beginning of January 2007, after the occurrence of new febrile episodes with stranguria and haematuria, the patient was once more admitted to the OU of Rheumatology; during the hospitalization, the diagnosis of UTI caused by P. mirabilis was made (the infection was treated with meropenem 1500 mg/die for 14 days) and echografic examination highlighted the presence of renal lithiasis.
Discharged the 16th January, the patient had repeated domiciliary renal colic with gallstone expulsion.
Starting from February the therapy with methotrexate (15 mg/week i.m.) was initiated and the dosage of metylprednisolone was tapered to 4+4 mg/die.

At the last control (March 2007), the patient appeared in good conditions; haematochemical tests confirmed the pANCA-Ab positivity and the ESR and CPR normal values.

DISCUSSION

In our case, as frequently referred for other similar cases (Gordon *et al.,* 1993), the course of the disease, subdivided into two clearly distinct phases according to clinical presentation, conditioned dramatically the time of diagnosis.
The diagnostic hypothesis of CSS was made only when the disease had progressed to an irreversible stage characterized by severe gastrointestinal impairment, while prodromic symptoms, including asthma attacks and rhinosinusitis episodes, had been ascribed to allergic *noxae*, though no risk factors susceptible to be associated with patient's working activity or lifestyle habits had been identified.
Probably steroid therapy, started early and protracted for months, contributed to mask initial signs of the disease, without blocking, however, its progression. In this case the diagnostic delay had particularly serious consequences, making two of the prognostic indexes considered among the most unfavourable ones in the evolution of CSS to converge: the co-localization of flogistic and necrotizing process in intestinal small- and medium-size arteries with multiple perforations of the small bowel, as well as the indication for one or more intestinal resections are, in fact,

pointed out by several Authors among factors associated with the highest risk of mortality in the course of the disease (Guillevin *et al.,* 1996).
The use of metylprednisolone-cyclophosphamide combination therapy allowed us to reach disease remission, allowing the patient to maintain a satisfactory quality of life over next months, despite the frequent occurrence of UTI; in particular, cyclophosphamide was administered by intravenous boluses in order to reduce the total dose of the drug, limiting in the meanwhile the incidence of side effects (which are mainly associated to protracted oral administration), included haemorragic cystitis and malignant neoplasia of the bladder.
The availability of these pharmacological associations induced a radical improvement in systemic vasculitis long-term prognosis, decisively contributing to transform these pathological entities from high mortality index acute diseases into chronic disorders whose course is characterized by alternant phases of activity and remission of symptomatology.
The most favourable perspectives in terms of survival, however, are accompanied by the emergence of new issues, the first of which is the constant risk of relapse, which can occur both during therapy and after treatment interruption, involving also organs and systems different from those affected in the previous episodes of the disease (D'Cruz *et al.,* 1999).
Furthermore, protracted therapeutic cycles of immunosuppressive and cytotossic agents lead to the occurrence of side effects, consisting most frequently in recurrent infections but also in neoplastic diseases or sterility.
The design of protocols which include the use of the lowest pharmacological dosages able to induce and maintain disease remission represents thus a primary target in the management of systemic vasculitis. It's worth noting the importance of a particularly strict monitoring of respiratory affections occurring for the first time during adult life which, in the hypothesis of an allergic pathogenesis, are treated for long periods with steroid drugs; indeed, cases of bronchial asthma or rhinosinusitis of late onset, with or without evidence of triggering factors, could be highly predictive of these pathologies, which not rarely manifest themselves concomitantly with the reduction of the steroid dosage used till that moment or after their interruption (Gordon *et al.*, 1933).
Periodic research of signs and symptoms of systemic involvement, including fever, weight reduction, arthromyalgias, peripheral neuropathies, rash, as well as the surveillance of specific inflammatory indexes , can thus represent a useful means for the early diagnosis and for the implementation of therapeutic measures able to induce a slower progression of the disease itself.

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