Transplant International ISSN 0934-0874

CASE REPORT

Successful liver transplantation and treatment of recurrent hepatitis C using pegylated alpha-interferon in a patient with Churg–Strauss disease

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Keywords
Churg–Strauss disease, hepatitis C virus, immunosuppression, liver transplant.

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*Hugo Bonatti was supported by the Detiger Fellowship.

Received: 19 July 2006
Revision requested: 5 September 2006
Accepted: 10 October 2006

doi:10.1111/j.1432-2277.2006.00415.x

Summary

Churg–Strauss disease (CSD) is a rare allergic disorder that is associated with vasculitis, peripheral eosinophilia and allergic asthma. We report on successful liver transplantation in a patient with CSD who suffered from chronic hepatitis C. Recurrent hepatitis C and CSD were ultimately managed by the application of pegylated interferon.

Introduction

Churg–Strauss disease (CSD), also known as allergic angiitis or granulomatosis, was first described in 1951. It is characterized by granulomatous angiitis, allergic rhinitis, asthma and prominent peripheral blood eosinophilia [1]. CSD is a systemic vasculitis that involves small- and medium-size blood vessels of the lungs, peripheral nerves and skin, but less frequently may affect any organ system, including the cardiovascular, kidney, gastrointestinal and central nervous system [1]. The exact etiology is unclear, but an autoimmune process is suggested based on the presence of T-cell and eosinophil activation [1–3]. There are no specific serologic markers for diagnosis, but striking peripheral blood eosinophilia is a characteristic finding. Both anti-neutrophilic cytoplasmic antibodies (ANCAs) positive and negative markers in CSD have been described [4]. Asthma is present in 95% of patients and may precede vasculitis by several years [1]. This prodomal phase is followed by an eosinophilic phase which is characterized by chronic pneumonitis and/or eosinophilic gastroenteritis. The third, vasculitic phase manifests with weight loss, fever, polyarthralgia, and may be accompanied by specific organ involvement [1]. Two-thirds of patients present with skin disease in the vasculitic phase, with lesions appearing on arms, hands and legs. Histological findings include extravascular eosinophilic infiltrations and necrotizing vasculitis. These findings confirm the diagnosis, with lung biopsy being the gold standard for the diagnosis [5].

Lung and cardiac transplantations have been described in patients with CSD but, to our knowledge, no liver

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transplantation has been performed in patients with this condition [6–8]. Patients with CSD and concomitant hepatitis C virus (HCV)-associated liver disease might be even less suitable candidates for liver transplantation as steroid maintenance therapy to suppress CSD may increase the risk for HCV recurrence and disease progression. This article describes the course of a successful liver transplantation in a patient with CSD and HCV-related liver disease.

Case report

The patient was a 57-year old woman, who was transferred to our liver transplant facility for end-stage liver disease (ESLD) secondary to HCV infection in September 2000. She was initially hospitalized 6 months previously for pneumonia, malaise, fever, chills, shortness of breath and confusion. During the following months, she was hospitalized two more times for pneumonia. The patient had been diagnosed with arthritis for which she had taken prednisone (5 mg every other day) for approximately 6 months. Her liver complications included encephalopathy, ascites and muscle wasting. On admission, she had fever up to 38.5 °C, chills and a diffuse palpable skin rash which she was noted to have prior to this admission. Punch skin biopsies revealed focal vasculitis with prominent neutrophils and eosinophils. There were no findings consistent with HCV-associated cryoglobulinemia. Vasculitis involved her extremities and was of a migratory nature for which she had been prescribed cetericine (Zyrtec®; Pfizer Inc., New York City, NY, USA) 3 weeks earlier. ANCAs were negative. The prednisone was held due to the presence of HCV. CT scan and ultrasound of the abdomen were consistent with liver cirrhosis. Echocardiography showed a normal left ventricular function, the ejection fraction was 70% and the right heart pressure was normal at 29 mmHg. The initial pulmonary function test (PFT) showed a forced expiratory volume (FEV) of 33% and a forced expiratory vital capacity (FVC) of 43%, FEV1/FVC ratio of 63.8 with a vital capacity of 44%, and oxygen saturation of 92%, indicating both obstructive and restrictive lung patterns. On her third night after admission, the patient experienced hematochezia and emergency esophagogastroduodenoscopy (EGD) showed grade IV esophageal varices and gastric varices as well as erosive gastritis without evidence of bleeding or vasculitis. Colonoscopy showed no vasculitis and no source of bleeding. She continued to have spiking fevers at night. Results of thoracocentesis fluid obtained the day of admission showed WBC of 350 cells/μl with 74% eosinophils. Peripheral eosinophilia, dense pulmonary infiltrates on the CT scan, eosinophilia on the pleural fluid and focal eosinophilic vasculitis on skin biopsies confirmed the diagnosis of CSD. Oral steroid therapy was resumed and testing for candidacy for liver transplantation proceeded. The patient continued to spike temperatures and remained short of breath despite steroid therapy. CT scan demonstrated recurrence of the right pleural effusion and thoracentesis was repeated. Bone marrow aspiration showed normal erythropoiesis and increased granulopoiesis with a left-shifted maturation and approximately 10% eosinophils consistent with reactive hypereosinophilic syndrome. PFTs did not improve after steroid therapy. A flexible bronchoscopy showed normal lung parenchyma. The patient was deemed to be a good candidate for liver transplantation if the pulmonary infiltrates were to continue to improve. She was treated with oral prednisone 30 mg daily and continued to improve. She was discharged 15 days after the initial admission with decreased ascites, pleural effusions and marked improvement on her vasculitic rash. PFTs were repeated after 2 and 4 weeks revealing significant improvement, but required hospitalizations again due to shortness of breath.

On November 4, 2000, the patient underwent liver transplantation with a United Network of Organ Sharing status 2A and Model of End-Stage Liver Disease score of eight. She received an allograft from a 28-year-old donor. The explant specimens of the native liver showed grade I, stage IV cirrhosis compatible with chronic hepatitis C, but no signs of active vasculitis. Her postoperative recovery was uneventful except for mild pulmonary edema, which responded well to diuretic therapy. Immunosuppression consisted of tacrolimus (TAC; Prograf®; Fujisawa Health Care, Inc., Deerfield, IL, USA), mycophenol mofetil (MMF; Cellcept®; Hoffmann-La Roche Ltd, Basel, Switzerland) and a steroid taper. Prednisone was maintained at 5–10 mg/day; MMF was weaned off at 4 months post-transplant. The patient developed neurotoxicity with prominent bilateral extremity tremor and was converted from TAC to cyclosporine A (CsA; Neoral®; Novartis International AG, Basel, Switzerland) with trough levels of 200–250 ng/ml) 2 months post-liver transplantation (LT). With CsA levels dropping below 50 ng/ml on one occasion, her blood eosinophilia recurred, which normalized again after adequate trough levels were achieved. Two years post-LT, the patient was readmitted to the hospital with symptoms of polyarthralgias, which were successfully treated with an increased dose of prednisone (20 mg daily). She has not had any evidence of recurrent CSD since then with a maintenance dose of 5–10 mg. Steroid therapy was complicated by the development of diabetes mellitus, Cushing syndrome and severe osteoporosis. Recurrence of HCV was noted on serum HCV RNA levels, elevated liver enzymes and liver

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biopsy (grade II/IV, stage 0/IV) as early as 2 months post-LT. No treatment for HCV was initiated with interferon therapy in view of the underlying CSD, mild histological activity and neuropsychiatric issues. Protocol liver biopsies at 1 and 2 years demonstrated no histological change. However, protocol liver biopsy at 3 years follow-up revealed grade II/IV, stage I/IV recurrent hepatitis C and by 4 years there was progression grade III, stage IV. Therefore, the patient was started with pegylated interferon (Pegasys®; Roche) at a dosage of 180 μg/week and ribavirin (Copegus®; Roche) at a dosage of 200 mg twice daily. The patient was able to complete 1-year treatment with a successful end of treatment response and has remained with undetectable HCV RNA for more than 12 months. Treatment for HCV was generally well tolerated except for anemia and neutropenia, for which granulocyte stimulating factor (GCSF; Neupogen®; Amgen Inc., Thousand Oaks, CA, USA) and epoetin alfa (Procrit®; Ortho Biotech Products, L.P., Raritan, NJ, USA) were given. Figure 1 displays the longitudinal laboratory values of the patient. The patient did not have other interferon-induced adverse events and in particular no flare of her CSD. The patient is currently alive at 5.5 years post-LT with normal graft function despite the presence of cirrhosis and her previous CSD. She does suffer from obesity, Cushing syndrome, new-onset diabetes mellitus and osteoporosis and currently requires 7.5 mg of prednisone.

Discussion

The concurrence of CSD and hepatitis C has previously been reported [9–11]. However, whether this is pure coincidence or if there may be interdependency remains unclear. This is the first report of an HCV patient suffering from CSD who underwent a successful liver transplantation. Recurrence of CSD in lung and cardiac transplantations has been reported, and CSD has also been shown to recur within the allografts [6–8]. CSD does in very rare cases present in the hepatic artery, which may affect the liver allograft [12]. CSD can also affect the hepatobiliary system causing hepatic abscesses, granulomatous hepatitis and cholangiopathy [13–16]. In our case, no CSD-related graft complications were observed and the vasculitis completely resolved with the

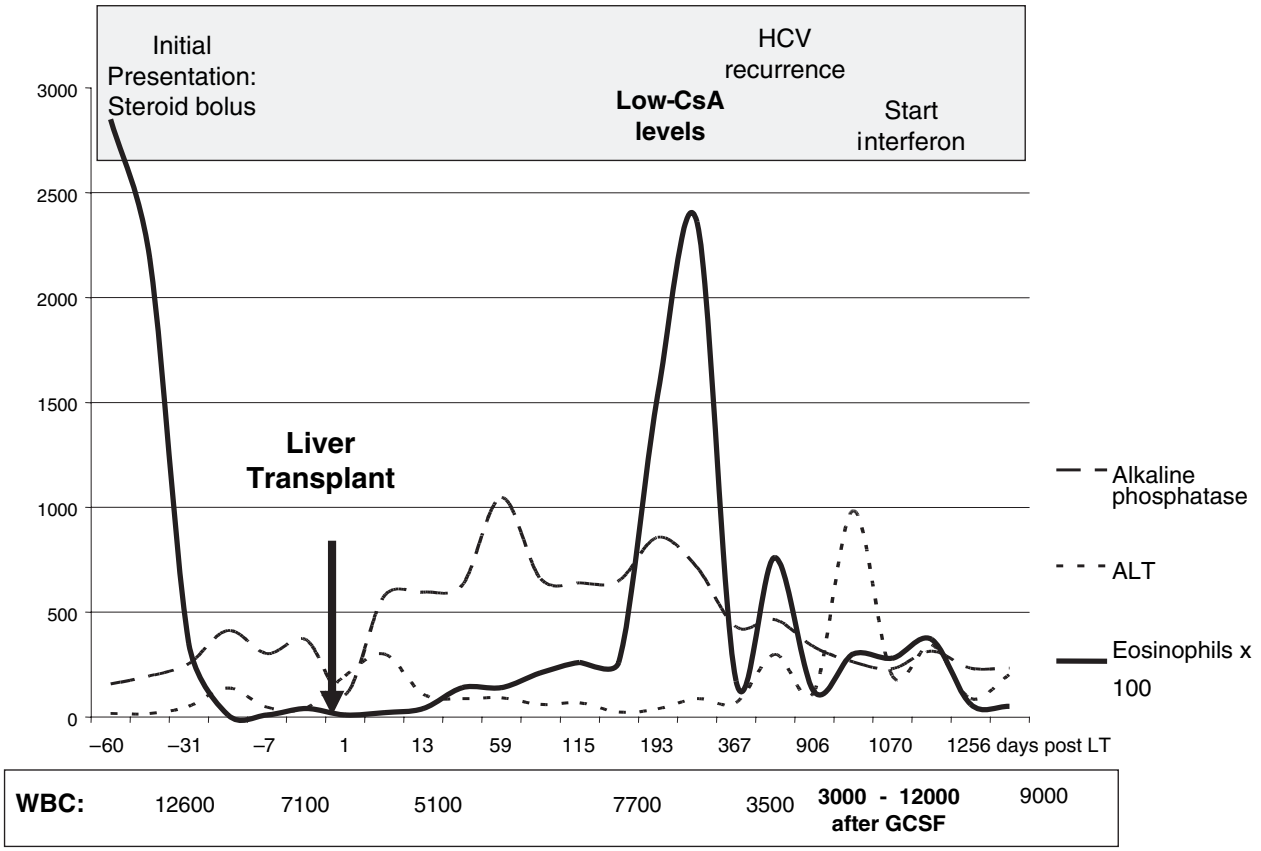

Figure 1 Clinical course and course of eosinophil count and liver enzymes: the drop in the eosinophilic count was not as a result of interferon induced neutropenia; following application of granulocyte stimulating factor (GCSF) the white blood cell count became normal but the eosinophilic count remained low.

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introduction of immunosuppression after LT. Prednisone therapy was increased prior to LT, which resulted in a significant improvement in the patient's condition, in particular, in the pulmonary function, which is vital during an extensive surgical procedure such as a liver transplantation [17]. Liver transplantation has evolved as the treatment of choice for ESLD. HCV-associated liver disease is the most common indication for LT in the USA [18,19]. The outcome in LT is excellent with 5-year survival rates of 70–80% [20]. The most limiting factors for the outcome of LT are: underlying co-morbidities, in particular, metastatic cancer, cardiovascular diseases and pulmonary disorders [21]. Pneumonia continues to represent as one of the leading causes of death [22] and pulmonary disorders remain a major cause of morbidity and mortality in patients after LT.

Churg-Strauss disease has been classified for prognostic and treatment purposes. CSD classification includes six criteria: asthma, eosinophilia, peripheral neuropathy, pulmonary opacities detected radiographically, paranasal sinus abnormality and tissue biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas; four or more of these criteria should yield diagnosis of CSD [5]. Baseline therapy consists of steroids, and cyclophosphamide, azathioprine and methotrexate have been used for maintenance and steroid-sparing purposes [1] CsA and MMF have recently been proposed as alternative therapies [23–25]. For severe cases of CSD, autologous stem cell transplantation has been performed [26]. Recent reports suggested interferon-α as an effective treatment of CSD [27–29]. To the best of our knowledge, pegylated interferon thus far has not been used in the treatment of CSD. As a measurement of CSD activity, blood eosinophilia may be useful. In our patient with the initiation of high-level immunosuppression pre-LT and early post-LT, eosinophilia dropped from 30% to less than 1% and rose again to normal values after taper of immunosuppression. Interestingly, during an episode of low CsA levels, a spike in the eosinophilic count was observed. Ultimately, with the introduction of pegylated interferon, the eosinophilic count dropped to subnormal values. The role of steroid therapy in HCV patients after LT has been identified as a major risk factor for HCV recurrence. In fact, steroid-free regimens for these patients have been proposed [30]. Recently, living-related small bowel transplantation from a twin brother in a patient with CSD causing intestinal necrosis was reported [31]. In this case, however, minimal immunosuppression post-transplant may be required to control CSD, but not for prevention of rejection of the HLA identical graft.

This case illustrates that CSD is not a contraindication to pursue liver transplantation. We also believe that immunosuppressive therapy can be used in patients with CSD prior to transplantation to minimize vasculitis which may prevent vascular complications after LT. The application of interferon as an alternative to recommended strategies in individuals without HCV infection is most appealing in this patient as this agent is an accepted therapy for both recurrent HCV and CSD [32]. This is the first report on the application of pegylated interferon for the treatment of recurrent HCV infection after liver transplant in a patient with CSD. Our patient is alive and now for more than 5 years with no evidence of recurrent CSD and no progression of her HCV within the allograft. Her current steroid requirement is 7.5 mg of prednisone.

References

1. Abril A, Calamia KT, Cohen MD. The Churg Strauss syndrome (allergic granulomatous angiitis): review and update. *Semin Arthritis Rheum* 2003; **33**: 106.
2. Schmitt WH, Csernok E, Kobayashi S, Klinkenborg A, Reinhold-Keller E, Gross WL. Churg–Strauss syndrome: serum markers of lymphocyte activation and endothelial damage. *Arthritis Rheum* 1998; **41**: 445.
3. Cottin V, Tardy F, Gindre D, Vernet G, Deviller P, Cordier JF. Urinary eosinophil-derived neurotoxin in Churg–Strauss syndrome. *J Allergy Clin Immunol* 1995; **96**: 261.
4. Guillevin L, Cohen P, Gayraud M, Lhote F, Jarrousse B, Casassus P. Churg–Strauss syndrome. Clinical study and long-term follow-up of 96 patients. *Medicine (Baltimore)* 1999; **78**: 26.
5. Masi A, Hunder G, Lie J, *et al.* The American college of rheumatology 1990 criteria for the classification of Churg–Strauss syndrome (allergic granulomatosis and angitis). *Arthritis Rheum* 1991; **33**: 1094.
6. Thomson D, Chamsi-Pasha H, Hasleton P. Heart transplantation for Churg–Strauss syndrome. *Br Heart J* 1989; **62**: 409.
7. Yeatman M, McNeil K, Smith JA, *et al.* Lung Transplantation in patients with systemic diseases: an eleven-year experience at Papworth Hospital. *J Heart Lung Transplant* 1996; **15**: 144.
8. Henderson RA, Hasleton P, Hamid BN. Recurrence of Churg Strauss vasculitis in a transplanted heart. *Br Heart J* 1993; **70**: 553.
9. Dikensoy O, Bayram NG, Erbagci Z, Namiduru M, Filiz A, Ekinci E. Churg–Strauss syndrome in an HCV seropositive patient. *Int J Clin Pract* 2003; **57**: 439.
10. Lamprecht P, Reinhold-Keller E, Gross WL. Hepatitis C infection, cryoglobulinemia, and Churg–Strauss syndrome. *J Rheumatol* 2000; **27**: 2721.
11. Mercie P, Viallard JF, Faure I, *et al.* Hepatitis C virus infection with and without cryoglobulinemia as a case of Churg–Strauss syndrome. *J Rheumatol* 2000; **27**: 814.

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12. Nakamura S, Yokoi Y, Suzuki S, *et al.* A case of melena caused by a hepatic aneurysm ruptured into the intrahepatic bile duct in a patient with allergic granulomatous angiitis. *Jpn J Surg* 1991; **21**: 471.
13. Gambari PF, Ostuni PA, Lazzarin P, Fassina A, Todesco S. Eosinophilic granuloma and necrotizing vasculitis (Churg–Strauss syndrome?) involving a parotid gland, lymph nodes, liver and spleen. *Scand J Rheumatol* 1989; **18**: 171.
14. Otani Y, Anzai S, Shibuya H, *et al.* Churg–Strauss syndrome (CSS) manifested as necrosis of fingers and toes and liver infarction. *J Dermatol* 2003; **30**: 810.
15. Brooklyn TN, Prouse P, Portmann B, Ramage JK. Churg–Strauss syndrome and granulomatous cholangiopathy. *Eur J Gastroenterol Hepatol* 2000; **12**: 809.
16. Conn DL, Dickson ER, Carpenter HA. The association of Churg–Strauss vasculitis with temporal artery involvement, primary biliary cirrhosis, and polychondritis in a single patient. *J Rheumatol* 1982; **9**: 744.
17. Aduen JF, Stapelfeldt WH, Johnson MM, *et al.* Clinical relevance of time of onset, duration, and type of pulmonary edema after liver transplantation. *Liver Transpl* 2003; **9**: 764.
18. Machicao VI, Krishna M, Bonatti H, *et al.* Hepatitis C recurrence is not associated with allograft steatosis within the first year after liver transplantation. *Liver Transpl* 2004; **10**: 599.
19. Machicao VI, Bonatti H, Krishna M, *et al.* Donor age affects fibrosis progression and graft survival after liver transplantation for hepatitis C. *Transplantation* 2004; **77**: 84.
20. Burroughs AK, Sabin CA, Rolles K, *et al.* 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *Lancet* 2006; **367**: 225.
21. Mark W, Graziadei I, Bargehr D, *et al.* Infectious complications limit the outcome of liver transplantation in medical urgency code 2 patients. *Transplant Proc* 2005; **37**: 1224.
22. Aduen JF, Hellinger WC, Kramer DJ, *et al.* Spectrum of pneumonia in the current era of liver transplantation and its effect on survival. *Mayo Clin Proc* 2005; **80**: 1303.
23. McDermott EM, Powell RJ. Cyclosporin in the treatment of Churg–Strauss syndrome. *Ann Rheum Dis* 1998; **57**: 258.
24. Assaf C, Mewis G, Orfanos CE, Geilen CC. Churg–Strauss syndrome: successful treatment with mycophenolate mofetil. *Br J Dermatol* 2004; **150**: 598.
25. Gross WL. New concepts in treatment protocols for severe systemic vasculitis. *Curr Opin Rheumatol* 1999; **11**: 41.
26. Kotter I, Daikeler T, Amberger C, Tyndall A, Kanz L. Autologous stem cell transplantation of treatment-resistant systemic vasculitis–a single center experience and review of the literature. *Clin Nephrol* 2005; **64**: 485.
27. Simon HU, Seelbach H, Ehmann R, Schmitz M. Clinical and immunological effects of low-dose IFN-alpha treatment in patients with corticosteroid-resistant asthma. *Allergy* 2003; **58**: 1250.
28. Termeer CC, Simon JC, Schopf E. Low-dose interferon alfa-2b for the treatment of Churg–Strauss syndrome with prominent skin involvement. *Arch Dermatol* 2001; **137**: 136.
29. Tatsis E, Schnabel A, Gross WL. Interferon-alpha treatment of four patients with the Churg–Strauss syndrome. *Ann Intern Med* 1998; **129**: 370.
30. Nair S, Loss GE, Cohen AJ, Eason JD. Induction with rabbit antithymocyte globulin versus induction with corticosteroids in liver transplantation: impact on recurrent hepatitis C virus infection. *Transplantation* 2006; **81**: 620.
31. Schena S, Testa G, Setty S, Abcarian H, Benedetti E. Successful identical-twin living donor small bowel transplant for necrotizing enterovasculitis secondary to Churg–Strauss syndrome. *Transpl Int* 2006; **19**: 594.
32. Tierney LM, McPhee SJ, Papadakis MA. *Current Medical Diagnosis and Treatment*. McGraw-Hill Publishing Co.; 46th Edition, 2006: p. 292.

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