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CASE REPORT

Successful identical-twin living donor small bowel transplant for necrotizing enterovasculitis secondary to Churg–Strauss syndrome

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Summary

Churg–Strauss syndrome (CSS) is a granulomatous small-vessel vasculitis with unknown etiology. Extra-pulmonary manifestations of CSS are currently treated with a combination of steroids and Cyclophosphamide. Its gastrointestinal complications may be devastating, occasionally requiring extensive bowel resection resulting in short-gut syndrome. Living-related small bowel transplantation (LRSBTx) is a relatively standardized procedure that, not only represents a valid alternative to cadaver bowel transplant in selected cases, but also portraits excellent results when performed in experienced centers. The availability of an identical twin as a donor, which allows avoidance of immunosuppressive therapy, is a major indication for this procedure. We present the case of a young individual affected by gastrointestinal necrotizing vasculitis that lost almost his entire small bowel requiring the immediate institution of total parenteral nutrition (TPN). However, within few weeks a significant hepatic dysfunction ensued. An identical twin-brother, not affected with CSS, became an immediate, optimal donor-candidate for LRSBTx, the first of this kind in a patient affected with CSS. Following the procedure, two main concerns were addressed: the recipient's ability to recover a regular intestinal function without immunosuppression and the possible recurrence of the primary disease. Twenty-seven months post-transplant, the patient enjoys a regular lifestyle without any clinical, endoscopic and histologic evidences of recurrent disease in the transplanted graft.

Case report

A 33-year-old asthmatic male presented with dyspnea, abdominal pain, hematochezia, rash involving all the extremities and leukocytosis (25 200/mm^3) with marked eosinophilia. A CT-scan showed numerous intestinal segments with intraparietal gas and impending perforation, therefore he underwent exploratory laparotomy. Intraoperatively, microabscesses involving the gallbladder were also observed. Therefore, cholecystectomy and resection of the entire small bowel, with the exception of 5 cm of proximal jejunum and 10 cm of terminal ileum, were performed. Punch biopsies of the skin rashes were obtained. Interestingly, the microscopic examination of the specimens showed significant granulomatous vasculitis involving muscular, medium-sized arteries resulting in acute, transmural, and ischemic necrosis of the small bowel, appendix and gallbladder. The relevant findings consisted in vessel lumina almost entirely obliterated by fibrinoid necrosis and perivascular eosinophil-predominant inflammation (Fig. 1a). A Jones' silver staining highlighted a diffuse destruction of the elastic fibers causing discontinuity of the media layer (Fig. 1b). The skin biopsy demonstrated mild perivascular inflammatory reaction with

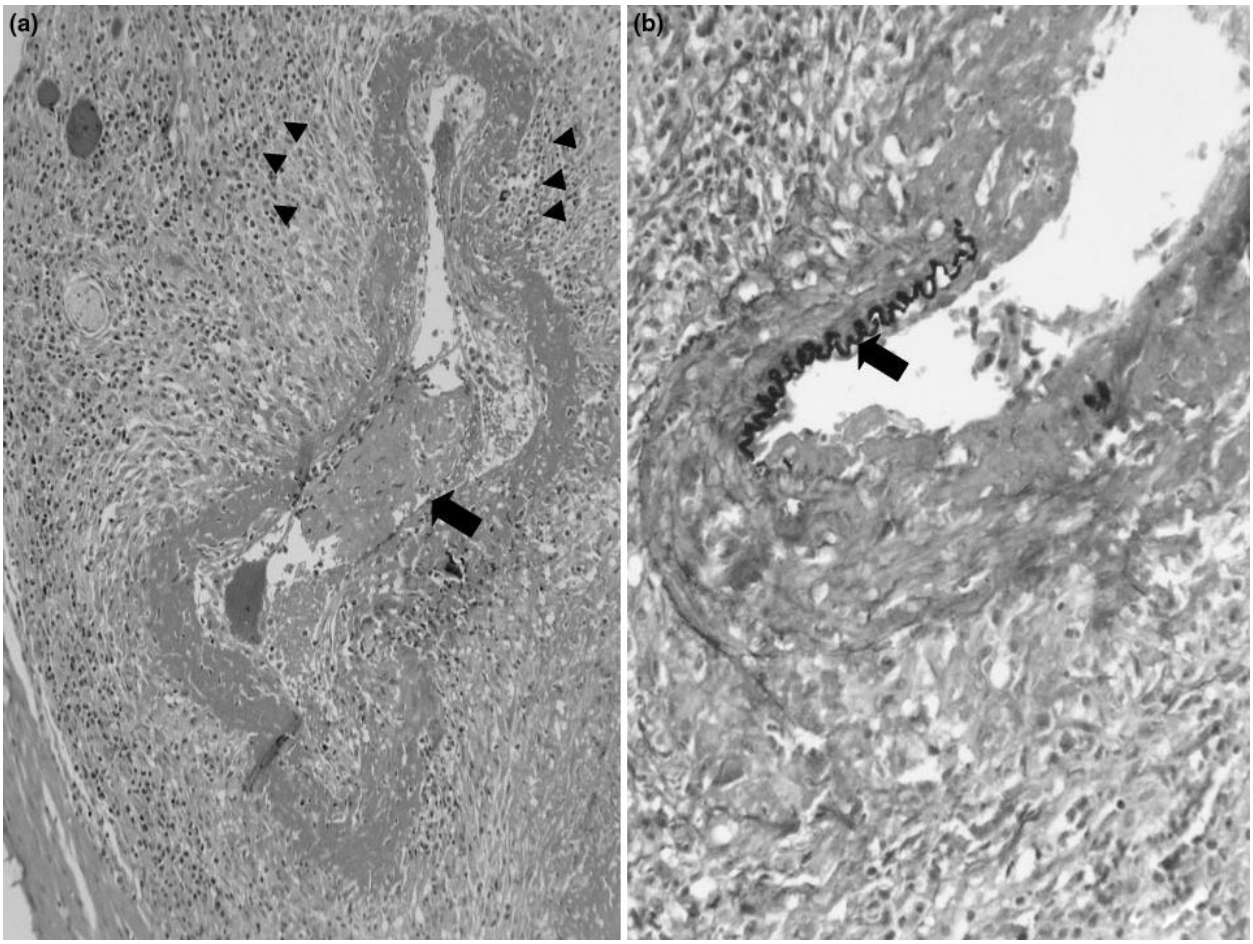

Figure 1 (a) HE staining of resected small bowel (×20) vessel lumina almost entirely obliterated by fibrinoid necrosis (black arrow) and perivascular eosinophil-predominant inflammation (black tips). (b) Jones' silver staining specifically highlighted a diffuse destruction of the elastic fibers causing discontinuity of the media layer.

abundant eosinophilia. The co-existence of asthma, peripheral eosinophilia with infiltration of multiple organs and granulomatous, necrotizing vasculitis of the medium-sized arteries led to the final diagnosis of CSS.

Due to a nearly total small bowel loss, the patient developed short-gut syndrome requiring long-term TPN. Within few weeks, the patient experienced a rapidly declining overall condition with severe weight loss and significant hepatic dysfunction (total bilirubin 3.8/INR 2.0), as well as two episodes of line sepsis. The patient had a liver biopsy showing cholestasis with minimal fibrosis and was therefore considered a candidate for isolated bowel transplantation (SBTx). At that stage, SBTx appeared to be a viable option. Interestingly, the patient had a healthy identical twin-brother (matched by high resolution DNA typing for HLA-A, B, C alleles at class I and DRB1 and DQB1 alleles at class II) willing to be tested as a donor and was immediately referred to be evaluated for LRSBTx. As a result of nature and unpredictable course of CSS, his case was reviewed with a panel of experts and analyzed for its possible long-term outcome. Both siblings were explained that such condition is autoimmune and was never treated with a transplant before. They were also made aware of the need for close follow-up because of possible late development of CSS in the donor, as well as chances of recurrence of the primary disease in the recipient, affecting the bowel graft. Both siblings agreed to proceed with the transplant given the ensuing hepatic dysfunction and worsening malnutrition of the patient.

The possibility that CSS might affect the donor-twin was appropriately ruled out with a thorough physical exam, rheumatology work-up (p-ANCA, c-ANCA, Protease 3 and MBO antibodies levels), bronchoscopic and endoscopic gastrointestinal evaluation. In the meantime, the recipient's respiratory performance and eosinophil count were optimized with Cyclophosphamide (600 mg/m^2

body surface) and high-dose steroids. The day of transplant, a 200-cm segment of terminal ileum was procured and transplanted, as previously described [1]. The donor recovered well, was discharged home within 3 days and does well 27 months later. The recipient's postoperative course was also uneventful; he indeed tolerated a regular diet within 10 days. A Prednisone tapered regimen and only three monthly doses of Cyclophosphamide, represented the immediate prophylaxis of recurrent CSS. He currently remains on a maintenance dose of 15 mg/day of Prednisone with no additional immunosuppression. Weekly biopsies of the intestinal graft failed to show recurrent disease, rejection, or other pathologies. At 27 months follow-up, the donor-twin is in good health with no signs or symptoms of CSS while the recipient is following an unrestricted general diet.

Discussion

Churg–Strauss syndrome (CSS) is a rare systemic vasculitis occurring in patients with asthma [2]. It is characterized by peripheral eosinophilia, eosinophilic infiltrates and elevated p-ANCA titers. Little is known about its cause and pathogenesis. However, the presence of a marked tissue- and blood-eosinophilia implicates a pathogenetic role for eosinophil granulocytes that seem to undergo prolonged survival as a result of inhibition of CD95-mediated apoptosis by soluble CD95 [3, 4].

Gastrointestinal involvement is quite frequent in patients with CSS: clinical symptoms (abdominal pain, diarrhea or bleeding) range from 44% to 89%, while pathologic involvement of the bowel is observed in 33–92% of the cases with features of granulomatous vasculitis, multiple colonic ulcers and small-bowel necrosis [5]. The most common causes of death in CSS are related to cardiac, neurological and renal complications [6].

Corticosteroids are the first-line therapy for all stages of the disease when active vasculitis needs to be treated rapidly. In patients with severe disease and organ- or life-threatening manifestations, the addition of Cyclophosphamide appears to improve the outcome and reduces the incidence of relapses [7]. However, if CSS is not promptly recognized and appropriately treated it can rapidly evolve in permanent organ damage.

In the last decade, SBTx has become a valuable option to treat selected patients affected by irreversible intestinal failure. TPN still represents the first managing option but cannot be administered without significant morbidity for a prolonged period. SBTx is an effective therapy for the treatment of those patients with intestinal failure who cannot tolerate parenteral nutrition [8]. Despite a relatively small number of candidates, the waiting time averages 90 days, and mortality remains elevated [9]. The latter can be partially explained with a trend for very late referral to SBTx when all the other options have been exhausted [10].

Currently, cadaver SBTx is considered only for patients with short-gut syndrome experiencing life-threatening complications of long-term TPN and it is rarely recommended immediately after extensive enterectomy. LRSBTx has been recently proposed as a viable alternative to cadaver transplantation in selected centers. Data from the Intestinal Transplant Registry have documented that patient and graft survival in the 32 cases of LRSBTx reported are comparable with those obtained using cadaver donors (http://www.intestinaltransplant.org/).

This particular case raises two important issues: donor selection and long-term control of the primary disease. In the judgment of the referring physicians, the availability of an identical twin-donor warranted the immediate evaluation for LRSBTx. The excellent results of living donor bowel transplant using identical twins as donor is well documented [11]. As the patient's small bowel anatomy was such to prevent any possible rehabilitation (<15 cm of residual length), and he was rapidly developing complications caused by TPN, a SBTx was in his best interest, in our opinion too. However, considering a LRSBTx in a recipient affected by a disease of uncertain etiology such as CSS, carries obvious risks both for the donor (i.e. resection of a long small bowel segment) and the recipient (i.e. recurrence of primary disease) that are hard to estimate. Moreover, the chance that the primary condition could develop later on in the healthy sibling's life has to be considered. The literature reports cases of patients benefiting of living-related grafts that have developed diseases either silently carried by donors [12] or that recurred in the recipient[13]. Both possibilities surely exist and should be carefully considered in planning this procedure.

In this particular case, the donor-twin underwent thorough investigations for the presence of CSS and, although completely asymptomatic, we could not completely exclude the future occurrence of the primary disease. The decision to proceed with LRSBTx was based on three main factors. First and foremost, the immediate need of a transplant based on the patient's clinical deterioration and poor tolerance to TPN. The patient was affected by ultra-short bowel syndrome with no hopes of rehabilitation. Enlisting this patient for a cadaver SBTx could have exposed him to progression to liver dysfunction/failure and recurrent line sepsis while on a waiting list. Intestinal transplantation is now a recognized therapeutic option with specific indications for patients with coexistent liver dysfunction.

A second important consideration was that CSS does not originate in the donated graft as an autoimmune

disease. We rather, protected the small bowel from the recipient's milieu by controlling the eosinophil count and the primary disease with low doses of steroids. The risk of recurrent disease in patients on chronic steroid therapy is very low [14]. Last but not least, we had the availability of a monozygotic twin-brother. Organ transplantation between monozygotic twins has been successfully performed before without immunosuppressive treatment [11,15]. We opted to avoid a full immunosuppression in consideration of the syngeneic nature of the small bowel graft and focused on standard medical therapy to prevent the recurrence of systemic disease in the recipient. More than 2 years later, the excellent clinical condition of both siblings seems to reward the decision made. However, a continuous follow-up will be necessary.

In conclusion, short-gut syndrome secondary to CSS can be successfully treated with SBTx. Availability of an identical twin-donor may represent an additional option and offers a perfect opportunity to avoid chronic immunosuppression and its risks. Steroid-based standard medical therapy for CSS is adequate to prevent recurrent disease in the transplanted graft.

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