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Sclerosing peritonitis, a rare complication after intestinal transplant. Report of one case successfully treated with adjustment of immunosuppression

Rumbo C, Zambernardi A, Cabanne A, Rumbo M, Gondolesi G. Sclerosing peritonitis, a rare complication after intestinal transplant. Report of one case successfully treated with adjustment of immunosuppression.

Abstract: Sclerosing peritonitis is a complication described in different clinical situations, such as patients that underwent prolonged peritoneal dialysis or renal transplantation with previous history of peritoneal dialysis. The origin of this entity is unclear so far and it is believed that several mechanisms may contribute to its development. The hallmark of sclerosing peritonitis is the continuous accumulation of fibrocollagenous deposits in the intestinal wall and mesenteries causing progressive adhesion of the intestinal loops and mesenteric retraction resulting in intestinal obstruction. Also, it has been described as a rare complication after intestinal transplant that might lead to graft failure. In this report, we describe a case of sclerosing peritonitis after intestinal transplantation that was successfully treated with modifications in the immunosuppressive regime allowing restitution of gastrointestinal transit and intestinal autonomy.

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SP is a rare complication after IT. Its origin is unclear, but it might lead to graft failure. The hallmark of SP is the continuous accumulation of fibrocollagenous deposits in the intestinal wall and mesenteries causing progressive adhesion of the intestinal loops and mesenteric retraction resulting in intestinal obstruction (1). Different degrees of vasculopathy and inflammatory infiltration can be also present in the serosa although minimal changes are observed in the mucosa, being consequently an entity that is impossible to diagnose by endoscopy and mucosal biopsies, usually used as the standard follow-up practice in the patients after IT (2, 3). SP has been described in other situations different to IT, such as prolonged peritoneal dialysis (4) or renal transplantation with previous history of peritoneal dialysis (5, 6). Also, there have been reports that associated SP with the use of beta blockers (7), and others have described it as a rare complication of systemic lupus erythematosus (8). The evidence reported so far indicates that it could be of multifactorial etiology and that several mechanisms may contribute to its development. Published data show that the prevalence rates in the general population are low, between 0.54% and 0.9% (9–11). So far, SP cases related to IT have been treated with partial intestinal resection or enterectomy leading to retransplantation (1–3). In some of these cases, adjustment of immunosuppression including corticosteroid boluses as palliative treatment was used, but in all cases, surgical resections were performed to solve the intestinal obstruction with high mortality associated with the occurrence of SP. In this report, we describe a case of SP after IT successfully treated with modifications in the immunosuppressive regime by inclusion of sirolimus and adjustment of tacrolimus and corticosteroid doses; this allowed long-term restitution of gastrointestinal transit and intestinal autonomy.

Abbreviations: IgE, immunoglobulin E; IT, intestinal transplant; PRA, panel-reactive antibodies; SP, sclerosing peritonitis.

Case

This is a seven-yr-old boy with long segment Hirschsprung's disease and lack of venous accesses that was evaluated for isolated IT. Due to high immunologic risk (3, 12) high – panel reactive antibody- in the pretransplant period, he underwent a desensitization protocol based on intravenous immunoglobulin, until the PRA become negative, and he underwent isolated IT with negative donor cross match. The transplant surgery was uneventful. The patient received induction immunosuppression with four doses of antithymocyte globulin, and the maintenance immunosuppression consisted of tacrolimus (blood levels 14–16 ng/mL), steroids, and mycophenolate mofetil. The patient started with enteral nutrition at day 6 post IT. During the second wk, the patient presented nausea and high ileostomy output. An upper endoscopy and ileoscopy were performed, and moderate acute rejection was diagnosed. The patient was treated with two steroid boluses; mycophenolate mofetil was discontinued, and sirolimus was started as third immunosuppressive drug. The enteral nutrition was then successfully increased, and the patient was sent home one month after IT. The parenteral nutrition was discontinued six wk after the transplant surgery. The protocol biopsies carried out monthly during the first yr of follow-up showed no abnormalities. The patient continued with tacrolimus and oral corticosteroids (prednisone) that were tapered down to 2 mg/day eight months after IT. Sirolimus was discontinued five months after transplant.

Twenty-three months after IT, the patient presented with persistent diarrhea and eosinophilia (total eosinophil count 3783/μL of blood), neutrophil count in peripheral blood was within normal limits. At that time, the immunosuppression consisted of tacrolimus and steroids at a minimal dose (prednisone 0.06 mg/k/day). The work-up done was negative for intestinal rejection and infectious gastroenteritis, including parasites. Intestinal biopsies were remarkable for eosinophilic infiltrates and minimal mononuclear infiltrates in the lamina propria (Fig. 1); no parasites were seen. The patient was noted to have very elevated total IgE, with class 3 specific IgE to egg and milk protein. He was placed on a restricted diet and the diarrhea improved, but the eosinophilia continued until the patient presented with bowel obstruction. Nine months after the eosinophilia started, the patient developed vomiting, decreased ostomy output, and weight loss. On physical exam, the terminal ileostomy showed erythema and was narrowed. Intestinal obstruction was suspected and confirmed with X-rays and computed tomography scan. The images showed a markedly dilated stomach and proximal jejunum with small amounts of air at different levels of the transplanted intestine (Fig. 2). The patient was operated finding the stomach and native jejunum dilated, with the transplanted bowel covered with dense fibrosis incarcerating it (Fig. 3); remarkably, the fibrotic process did not affect the native bowel. The fibrosis created multiple firm adhesions involving the graft only, which were impossible to release. Several peritoneal biopsies were obtained, a full thickness biopsy of the terminal ileum was carried out, and the ileostomy was revised (Fig. 4). The terminal ileum showed short and thick villi with no signs of acute

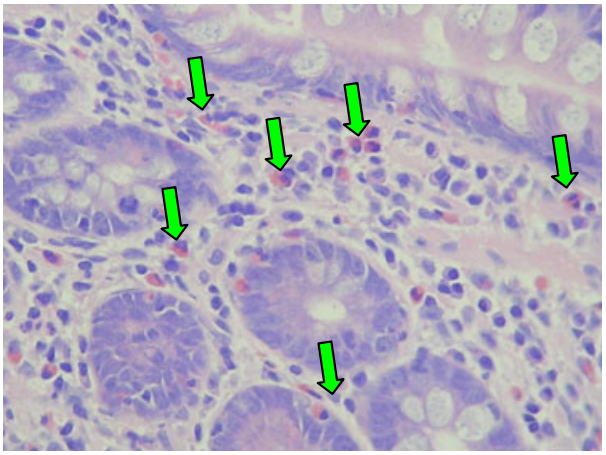

Fig. 1. Ileal biopsy obtained 23 months post IT. At that moment the patient presented persistent diarrhea and increased eosinophil count in peripheral blood. In the biopsy, increased eosinophils in the crypt epithelium and lamina propria can be observed (400 × magnifications).

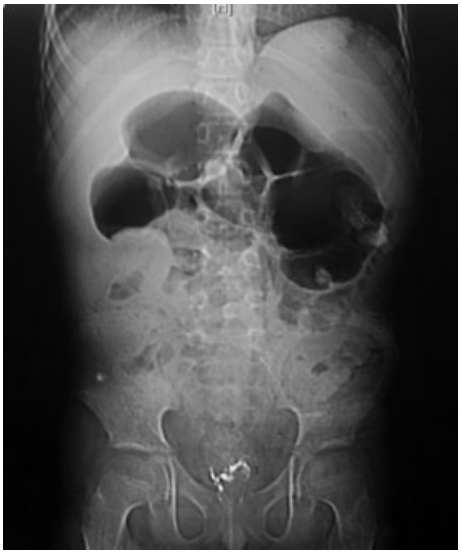

Fig. 2. Abdominal X-ray image taken at 32 months post-IT. Dilatation of the proximal bowel can be clearly appreciated, whereas the grafted intestine is completely collapsed.

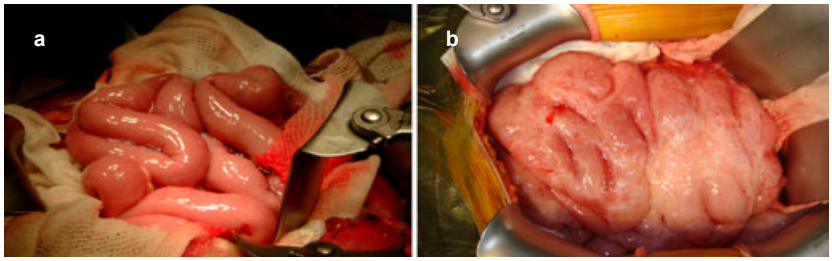

Fig. 3. Comparison of the macroscopic view of the intestine and peritoneum before and after the onset of peritoneal fibrosis. (a) Graft at the end of the transplant surgery. (b) Graft during laparotomy, 30 months after intestinal transplant (IT); the sclerosing peritonitis process is limited to the graft.

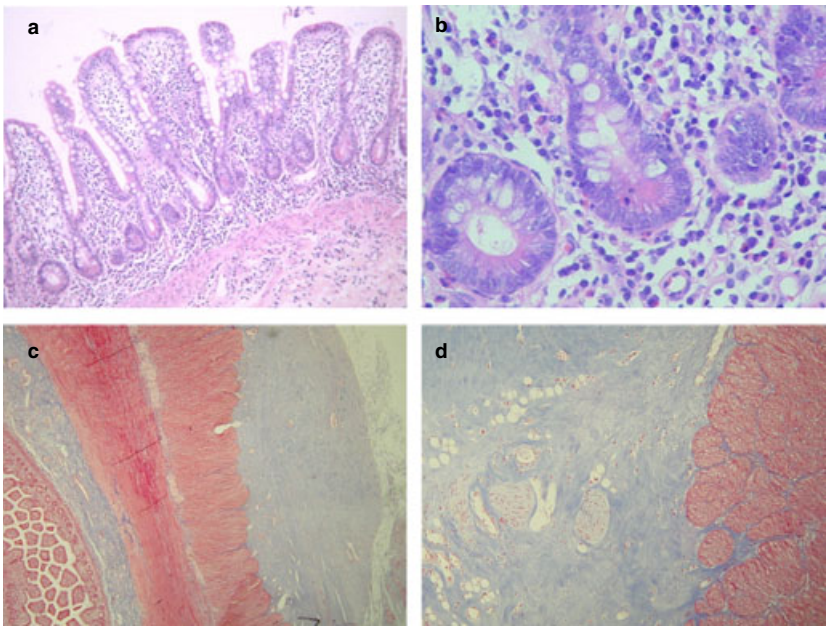

Fig. 4. Ileal biopsies taken at the surgery, 32 months after IT. (a) Mucosa and submucosa (100 ×) H&E staining. Shorten villi and augmented infiltration can be observed. (b) Mucosa with crypts and lamina propria (400 ×) H&E staining. Mixed infiltrate with presence of eosinophils can be observed. (c) Transmural intestinal biopsy (40 ×) Masson's trichrome stain. Significant collagen deposition in the small bowel subserosa is shown. (d) Serosa and muscular layers (200 ×) Masson's trichrome stain. Fibrous deposits intercalating into muscular fibers are shown.

rejection (Fig. 4a); the lamina propria was expanded showing a mixed infiltrate with the presence of eosinophils (Fig. 4b). The peritoneal side was covered with dense fibrosis. The peritoneal biopsies consisted of dense fibrosis resembling plastic peritonitis (Fig. 4c, d). Based on the histology and the surgical findings, the diagnosis of SP was made. Parenteral nutrition was started. The gastrostomy was left open to drain gastric secretions due to persistent intestinal obstruction. With the hypothesis of SP being an immunologic phenomenon that was only affecting the graft, the immunosuppressive regime was optimized. Oral steroids were significantly augmented (prednisone 1 mg/kg/day for six weeks and slowly tapered, see below), sirolimus was started, and tacrolimus levels were maintained between 6 and 8 ng/mL. During the following weeks, the patient recovered intestinal transit allowing intermittent and then permanent gastrostomy closure. The hypereosinophilia resolved immediately after the steroids were augmented, lowering the absolute eosinophil count from 3792 eosinophils/μL of blood to 253 eosinophils/μL in one week, remaining less than 180 eosinophils/μL since then. Two months after the increase in immunosuppression, the patient tolerated liquids by mouth, and then progressed to diet and enteral supplements, maintaining hydration and weight. At that point, corticosteroids were slowly tapered, bringing the dose from 1 to 0.05 mg/kg/day in six months; sirolimus and tacrolimus were maintained around a level of 6 ng/mL. The parenteral nutrition was slowly weaned and discontinued seven months after the change in immunosuppression. The intestinal follow-up biopsies were unremarkable. Total IgE remained elevated despite a restricted diet. Thirty months after instituting the change in the immunosuppressive protocol, the patient has maintained growth and intestinal sufficiency.

Discussion

IT is the established treatment for patients with chronic irreversible intestinal failure that has

developed serious complications related to parenteral nutrition support. In the post-transplant follow-up, several complications may arise; some of them are related to the use of immunosuppression such as infections or tumors, and others directly related to the graft, such as acute or chronic rejection (13). Other complications are not very well known due to its low frequency in the IT field; therefore, its diagnosis, etiology, risk factors, and treatment are not very well established.

SP is a rare entity that may arise after IT, consisting of progressive fibrosis and degeneration of the intestinal wall and mesenteries, clinically insidious and associated with high mortality (1–3). Here, we report a first case of SP occurring after IT that has been successfully treated with a combination of immunosuppressive drugs usually used for the post-IT management.

SP has been described in relation to peritoneal dialysis (4); in some cases, it was treated with beta blockers (6) or peritoneal–venous shunts (14). It has been suggested that minimal persistent bacterial translocation and chronic inflammation of the peritoneal cavity may trigger factors of this disease (15). There is a consensus that this may constitute the end stage of a progressive disease generated by the abovementioned factors, being clearly a multifactorial entity that is prompted by different causes.

An outstanding feature in this case of SP after IT is that the graft is affected by fibrosis, whereas the native intestine is preserved (1–3). This suggests that some alloreactive process may be the initial event that triggers the fibrosis. In our case, in concordance with the literature, diffuse infiltration of the intestinal wall was observed. Vasculopathy was not observed in all the cases reviewed, being, however, described as a concomitant feature of SP (1–3). Indeed, some of the reports describe the occurrence of SP as an end stage of chronic rejection (1), whereas other cases clearly were not associated with chronic rejection (2, 3), indicating that also in the setting of IT several causes may contribute to the occurrence of SP. In the case presented here, one clear finding that was not previously reported is the presence of eosinophilic infiltrates in the lamina propria, with the occasional presence of eosinophils in the external layers of the intestinal wall and mesenteries and persistent peripheral eosinophilia. The onset of peripheral eosinophilia and intestinal eosinophilic infiltration coincided with the onset of diarrhea and those events occurred several months before SP was diagnosed. An infectious cause could not be identified. The diarrhea was moderated by dietary restrictions although the increased number of eosinophils continued until the diagnosis of SP. Although not demonstrated, it is tempting to speculate that the chronic activation of an immune-mediated mechanism that includes eosinophils as the effector was responsible for the fibrosis observed. The eosinophilic infiltration disappeared once the immunosuppressive regime was changed, correlating with the reversal of the intestinal fibrosis and the restitution of the intestinal transit.

Eosinophils have been associated with fibrosis in multiple scenarios (16, 17). Eosinophils may contribute to tissue damage by the toxic effect of their granular content, leading to damage-induced fibrosis. Also, they produce several cytokines and mediators, such as transforming growth factor beta and fibroblast growth factor that are inducers of tissue repair and collagen deposition (18, 19). In the present case, the graft is affected by SP, whereas the native intestine remains unchanged; therefore, we speculated that an alloreactive process may be the initial event leading to SP. Eosinophils are associated with different forms of solid organ graft rejection (20), and there are animal models of chronic rejection that present similar findings than the ones reported in this case. Le Moine et al. (21) described a model of chronic skin allograft rejection characterized by graft fibrosis associated with diffuse eosinophilic infiltration. In this model, a major histocompatibility complex mismatched skin graft is implanted in mice treated with a single high dose of anti CD3 antibodies. Mice develop this pathology, that is, independent of antibodies and B cells (22); it is characterized by progressive collagen deposition and eosinophilic infiltrates. The authors show that this process is dependent on IL4 and IL5 and may be associated with vasculopathy and enhanced Th2 responses. In the case reported here, the use of sirolimus and the rise of tacrolimus and corticosteroids doses were decided as an alternative to enterectomy. Given the extension of the fibrotic lesions, an immunologic factor as the triggering agent was considered. Sirolimus is usually used as an elective drug to treat patients with IT (9), and it has been shown to inhibit fibrosis in different scenarios (23–25). Sirolimus has been used to treat SP in non-transplant patients (26, 27), and its efficacy to inhibit inflammation-driven SP in animal models has been proven (28, 29). In the present case, the immunosuppressive regime instituted consisted of sirolimus and adjustment of the tacrolimus and corticosteroids doses. Even though we have only indirect data regarding the improvement of the graft histopathology after treatment, the effects of the immunosuppression adjustment was clearly reflected by the eosinophils count in peripheral blood, the improvement in the

intestinal transit and the reacquisition of intestinal autonomy. All these data indicate the possibility that the fibrosis of the graft was at least partially resolved.

Conclusions

SP remains a rare entity that causes high morbidity, with several possible triggering factors. Improving our understanding on the physiopathologic mechanisms involved in this process will contribute to generate new treatment alternatives. In the present report, we described a successful management of the immunosuppressive regime used in an SP case that may contribute to increase the management alternatives when SP occurs in the post-transplant setting.

Authors' contributions

Carolina Rumbo – Acquisition, analysis, and interpretation of data; drafting the paper; approval of the submitted and final version. Agustina Zambernardi – Contribution in the data acquisition; drafting the paper; approval of the submitted and final version. Ana Cabanne and Gabriel Gondolesi – Substantial contributions to analysis of data; revising the paper; approval of the submitted and final version. Martin Rumbo – Substantial contributions to interpretation of data; drafting the paper and revising it critically; approval of the submitted and final version.

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