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LETTER TO THE EDITOR

Invasive thymic carcinoma in a patient with combined kidney–pancreas allograft – individual approach to diagnosis and treatment

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Malignancies are a major problem in organ transplant recipients, significantly affecting morbidity and outcome. Carcinogenesis in those patients has been associated with immunosuppressive therapy, which impairs immunologic integrity and leads to disruption of tumor surveillance [1]. Once a tumor has developed, outcome is worse in the transplant population and the approach remains controversial [2]. We here report primary successful treatment of an invasive thymic carcinoma in a patient with a solid kidney–pancreas transplant, while maintaining excellent graft function.

A 42-year-old man with type I diabetes for 31 years presented with severe, acute intractable abdominal pain. Fourteen months earlier, the patient had an uneventful combined kidney–pancreas transplant procedure. Induction therapy using basiliximab (cumulative dose 40 mg) and maintenance immunosuppression with tacrolimus, mycophenol mofetil (MMF) and methylprednisolone resulted in excellent graft function with serum creatinine levels of 1.0–1.2 mg/ml, normoglycemia, lack of glucosuria and an HbA1c of 6.0%. Regular follow-up visits with achieved target levels for tacrolimus of 8–12 ng/ml did not reveal any problems. Explorative laparotomy revealed covered bowel perforation, which was treated by hemicolectomy. Histologic evaluation demonstrated purulent fibrinoid peritonitis with lack of any evidence for lymphoma or another malignancy. After bowel perforation, immunosuppression with MMF was stopped.

During the pre-operative diagnostic procedures, a routine chest X-ray (Fig. 1a) surprisingly revealed a prominent mediastinal mass (arrowheads) and a left-sided pleural effusion (arrow). Computed tomography (CT, Fig. 1b) demonstrated a large left-anterior mediastinal tumor of $5 \times 4 \times 12$ cm (asterisk) with invasion of the pulmonary artery branch (arrowheads) and the pericardium (not shown) as well as a pleural effusion (arrow). Cytologic examination of the pleural effusion did not reveal malignant cells. Echocardiography showed tumor-induced compression of the left pulmonal veins with possible intraluminal infiltration and a hemodynamically nonrelevant medium-sized pericardial effusion; tumor infiltration of the myocardium could not be observed.

A CT-guided biopsy of the mediastinal mass yielded a solid specimen (Fig. 1c). Histopathologic analysis demonstrated sheets of undifferentiated cells with moderate anisocytosis (arrows), PAS-positive granular material in some tumor cells (not shown), lack of mucous production, and extensive areas of necrosis (asterisk), altogether suggest a necrotizing undifferentiated tumor. Immunohistologic staining demonstrated a strong positivity for cytokeratin and partly for vimentin and negative expression of thyroid transcription factor-1, α-fetoprotein, placentar alkaline phosphatase and chromogranin. A diagnosis of an undifferentiated thymic carcinoma (WHO type C) was made. Subsequent staging did not reveal any signs of distant metastasis, suggesting stage III according to the Masoka system.

Neoadjuvant polychemotherapy with vincristine, ifosfamide and prednisolone was initiated. Because of the intolerance to ifosfamide, therapy was switched to three courses with cisplatin, adriamycin and cyclophosphamide. To preserve graft function, the immunosuppressive regimen was maintained at reduced level (tacrolimus 2 mg b.i.d., methylprednisolone 4 mg q.d.). Re-staging after 5 months showed marked tumor regression with a residual tumor of 1.3 cm in diameter. Extensive surgery consisting of thymectomy, lymph node dissection, lung wedge resection and pericardectomy was performed 6 months after the initial diagnosis. Histopathologic analysis revealed tumor-free resection borders, and postsurgical staging with computed tomography was inconspicuous. During the 18 months of follow-up visits, the patient remained disease-free and both kidney and pancreas graft functions were stable with normoglycemia and a serum creatinine level of 1.0 mg/dl. Thereafter, the patient relocated and eluded follow-up visits.

Masses in the anterior mediastinum comprise a variety of pathologic entities and are likely to be malignant in more than 50% of cases [3]. One-third to half of all mediastinal tumors are detected incidentally and do not cause significant symptoms [4]. The most common

lesions are thymomas and thymic carcinomas, lymphomas, germ cell tumors, intrathoracic thyroid or parathyroid tissue, neuroendocrine tumors and metastases [5]. Discrimination of thymoma and thymic carcinoma is based upon radiographic appearance, metastatic behaviour and histopathology but may be difficult. In contrast to thymomas, thymic carcinomas have overtly malignant cytologic characteristics such as anaplasia, cellular atypia and increased proliferative activity. In addition, they tend to be more aggressive with evidence of invasion. Most of the thymic carcinomas are high-grade subtypes and histologically undifferentiated with a median survival of 15 months and a 5-year survival rate of 23% [6,7].

Although solid organ transplant recipients are at significantly higher risk to develop post-transplant malignancy [1], thymic carcinoma has not been described in this group so far. Therefore, an individual approach based on prognosis, feasibility and the patient's will was necessary. Induction therapy with a murine anti-CD3 antibody or monoclonal antilymphocyte antibody has been associated with post-transplant lymphoproliferative disorders (PTLDs) [8]. Basiliximab, a chimeric mouse-human monoclonal IL-2 receptor antibody, was also suspected to increase the risk for PTLD [9], although further investigations showed that rather maintenance therapy with an mTOR inhibitor than initial use of basiliximab was associated with development of PTLD [9,10]. With the thymus being a part of the lymphopoeitic system, it is conceivable that thymic neoplasia may be a specific form of PTLD. However, this does not apply to thymic carcinoma because of its epithelial origin. In the present case, pure coincidence seems to be more likely because the patient was at the same age for risk to develop thymic carcinoma as the general population [7]. Moreover, initial tumor size suggested tumor development before the transplant procedure. Nevertheless, immunosuppression may have facilitated tumor growth [11,12]. In the context of the patient's declared intention to keep his grafts, reduction of tacrolimus was a reasonable approach. As for thymic carcinoma, surgical resection in combination with platinum-based neoadjuvant chemotherapy [13] resulted in complete remission. However, a longer follow-up period is necessary to evaluate definite outcome.

In conclusion, we here report: (i) to our knowledge the first description of a thymic carcinoma in a solid organ transplant recipient; (ii) an encouraging primary outcome following neoadjuvant chemotherapy and extensive surgery; (iii) the option to maintain immunosuppression despite its potential to promote tumor development; and (iv) preserved excellent graft function of both transplanted kidney and pancreas organs in face of malignancy and nephrotoxic therapy. The present case encourages an individual approach with respect to tumor therapy and

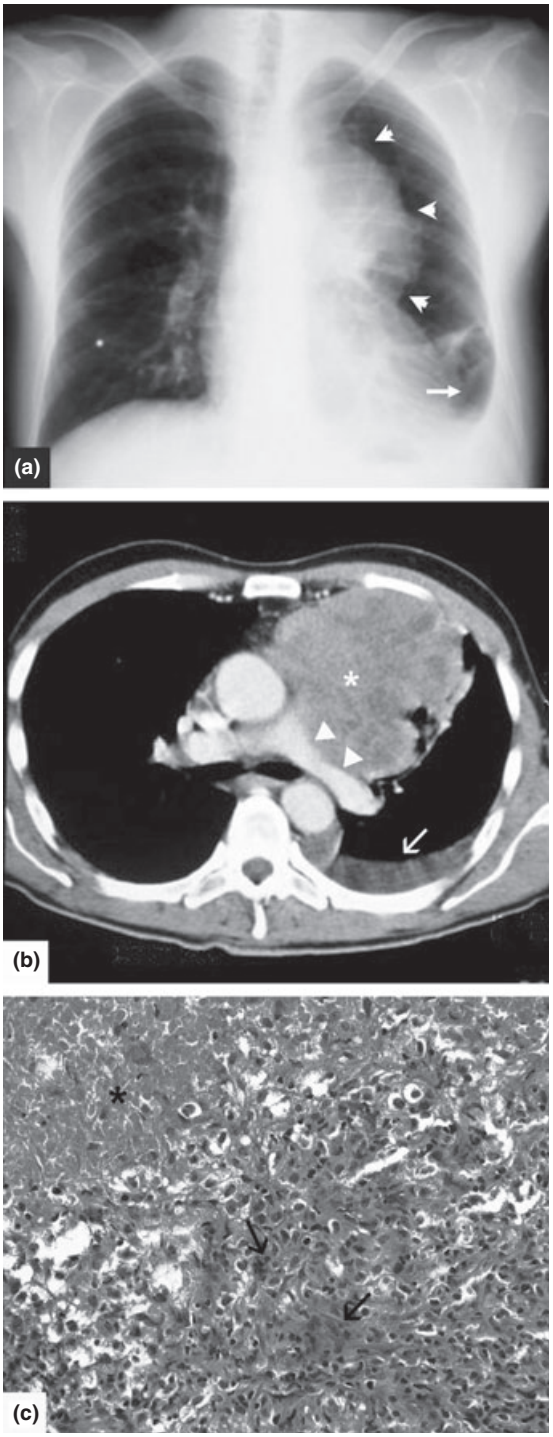

Figure 1 (a) Routine chest X-ray showing a prominent mediastinal mass (arrowheads) and a left-sided pleural effusion (arrow). (b) Computed tomography imaging showing a large left-anterior mediastinal tumor of 5 × 4 × 12 cm (asterisk) with invasion of the pulmonary artery branch (arrowheads) and a pleural effusion (arrow). (c) Histopathologic specimen of the tumor, demonstrating sheets of undifferentiated cells with moderate anisocytosis (arrows) and extensive areas of necrosis (asterisk), suggestive of a necrotizing undifferentiated tumor.

immunosuppressive regimen with legitimate hope for a favourite outcome despite the presence of a large, invasive and high-grade carcinoma.

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