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BRIEF REPORT

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Pulmonary aspergillosis masquerading as progressive post-transplant lymphoma

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Abstract We report a patient with post-transplant lymphoma who was treated by renal allograft nephrectomy, discontinuation of immunosuppressive therapy, and initiation of acyclovir administration. Despite these measures he appeared to have progressive lymphoma. Had a biopsy and cultures not been done, the diagnosis of aspergillosis would have been missed and the patient might have been treated with chemotherapy, with a potentially lethal outcome. Data from the Cincinnati Transplant Tumor Registry indicate that of 662 patients treated for post-transplant lymphoma, 277 patients died of cancer and 137 died of other causes, of which infection was a major factor. This case emphasizes the importance of proper work-up of patients with apparently progressive lymphomas.

Key words Aspergillosis, lymphoma · Lymphoma, aspergillosis

Introduction

Post-transplant lymphoma occurs in roughly 1 %–5 % of all solid organ transplant patients [7, 10–12]. While many cases remit if immunosuppression can be reduced, those that progress are often treated with cytotoxic chemotherapy and have a poor prognosis [3, 7, 10–13]. We briefly review the various treatments of lymphoma and report a case in which progressive lymphoid masses, following cessation of immunosuppression, were not due to progressive lymphoma, as initially believed, but rather to pulmonary aspergillosis. This case emphasizes the importance of evaluating lymphoma patients for other causes of progressive lymphadenopathy prior to initiating chemotherapy.

Case report

An 18-year-old male with end-stage renal disease secondary to complications of congenital diabetes insipidus underwent cadaveric renal transplantation. Immediate postoperative immunosuppression included corticosteroids, antithymocyte globulin, and cyclosporin. The patient was then discharged on cyclosporin, azathioprine, and prednisone. Two months later he was treated for 3 days with intravenous methylprednisolone followed by a 10-day course of anti-CD3 (OKT3) antibody therapy for allograft rejection. Cyclosporin, azathioprine, and prednisone were continued and he was well until 6 months post-transplantation, when an abdominal ultrasound revealed ureteral obstruction by a renal allograft-based mass. A computed tomography (CT) scan revealed a 4 cm × 6 cm × 6 cm mass within the renal allograft and shotty retroperitoneal lymphadenopathy; a plain chest radiograph was normal. Transplant nephrectomy was performed with incomplete tumor resection. Histology showed large lymphoid cells intermixed with small lymphocytes and plasma cells consistent with a diffuse, large

cell lymphoma. Immunoglobulin gene rearrangement studies revealed a monoclonal B-cell lymphoma. In situ hybridization studies for Epstein-Barr virus (EBV) were positive.

All immunosuppressants were discontinued. Intravenous acyclovir was initiated. A staging chest CT scan showed shotty (< 1 cm) pretracheal and subcarinal lymphadenopathy and a right hilar mass (3 cm). Over the following 6 weeks intravenous acyclovir was continued and the patient noted occasional low-grade fevers and mild fatigue. A repeat chest and abdominal CT scan revealed extensive, expanding mediastinal (2 cm), right hilar (10 cm), and retroperitoneal (1 cm) lymphadenopathy, a radiographic pattern termed "consistent with progressive lymphoproliferative disorder". Bronchoscopy was performed prior to initiation of chemotherapy. Transcarinal biopsy revealed normal, reactive lymph node tissue. Bronchoalveolar lavage was performed and results were negative for the following: cytology, viral culture and antigen tests, acid-fast bacterium stain and culture, toluidine blue stain for *Pneumocystis carinii* and *Legionella* culture. One colony-forming unit of *Aspergillus fumigatus* grew out of the tracheal aspirate; fungal stains were negative. Over the next 10 days the patient developed a dry cough and remained febrile to 38 °C. A repeat chest CT scan showed new bilateral pulmonary nodules with a diameter of 5–15 mm. Given that only one colony grew out of the tracheal aspirate, fungal stains were negative, and the radiographic appearance was not typical for *Aspergillus* pneumonia, upper respiratory colonization and culture contamination could not be ruled out. Repeat bronchoscopy with transbronchial lung biopsy revealed focal alveolar fibrosis with histiocytic proliferation, without evidence of lymphoma. The cultures and stains listed above were all negative except for one additional colony-forming unit of *Aspergillus fumigatus*. Eosinophilia was not present and antifungal antibody levels were not felt to be clinically useful.

Amphotericin was initiated and continued until a cumulative dose of 1.5 g was delivered. Within the first 10 days of antifungal therapy, the patient's fever and cough resolved and the infiltrates on plain chest radiograph improved. After 4 weeks of amphotericin the mediastinal, hilar, and retroperitoneal lymphoid masses were markedly decreased; the lung nodules also decreased in size and number. The patient remains well without evidence of lymphoma 3 months after treatment with amphotericin.

Discussion

In spite of halting all immunosuppression in this patient, mediastinal, hilar, and retroperitoneal lymphadenopathy continued to expand. These findings were highly suggestive of progressive lymphoma. The intrathoracic abnormalities in this patient are similar to those in transplant patients with intrathoracic lymphoma described in the literature. The most common radiographic manifestations in the series by Dodd et al. included pulmonary nodules with or without mediastinal or hilar adenopathy [4]. In retrospect, given the eventual diagnosis of aspergillosis, cytotoxic chemotherapy might have had disastrous consequences in this patient. Progressive pulmonary aspergillosis would have been potentiated by chemotherapy-induced neutropenia. The diagnosis of aspergillosis might have been delayed while clinical worsening would have been attributed to progressive lymphoma.

Lymphoma occurs in roughly 1 % of all renal allograft recipients [6, 7] and appears related to EBV-stimulated B-cell proliferations in the setting of profound T-cell suppression [2, 6–8]. The most important predisposing factor appears to be the duration and intensity of immunosuppression, regardless of the specific agents used [7, 10–13]. The proliferation can be polyclonal or monoclonal [1, 6, 7, 10–12] and either can regress in response to decreasing immunosuppression [7, 10–13]. For example, the Cincinnati Transplant Tumor Registry (CTTR) noted complete remissions in 52 of 169 patients treated with decrease or cessation of immunosuppression only [10–12]. In spite of reductions in immunosuppression, patients with progressive disease are often treated with cytotoxic chemotherapy and have a poor prognosis [7, 10–13].

Of 854 patients reported to the CTTR, 155 had no treatment and in 37 the therapy is unknown, leaving 662 patients who received various treatments (Table 1). Localized lymphomas may be successfully excised or treated with radiation therapy. A significant proportion of more extensive lesions have regressed partially or completely following reduction or cessation of immunosuppressive therapy [7, 10–13]. In particular, in recipients with widespread or extensive or potentially life-threatening lymphomas, all immunosuppression should be stopped except for a minimal dose of prednisone – 5–10 mg/day – until all evidence of lymphoma has disappeared. Allograft rejection may not occur or may occur slowly in chronic fashion, as many patients with lymphomas are very heavily immunosuppressed and a long time may be needed for immunocompetence to be restored. Once the lymphoma has regressed, immunosuppressive therapy should be resumed in a small dose and then gradually increased to maintenance levels.

Often lymphomas respond to multimodality therapy, which may include excision, radiation therapy, reduction of immunosuppression, acyclovir or ganciclovir administration to control an associated EBV infection, and treatment with interferon-alpha [7, 11, 12]. Chemotherapy is reserved for patients who do not respond to these measures. It is not well tolerated in these heavily immunosuppressed patients, as chemotherapy itself is immunosuppressive. In consequence, the lymphoma may vanish following chemotherapy, but the patient may die of an uncontrollable infection or of other complications of chemotherapy [12].

Up to 40 % of all infections in solid organ transplant recipients are fungal, and *Aspergillus fumigatus* is second only to *Candida* species as a cause of infection in these patients [5, 9]. Approximately 20 % of all fungal infections in renal transplant patients are secondary to *Aspergillus* [9]. *Aspergillus* pneumonia in an immunocompromised patient is classically a rapidly invasive, necrotizing bronchopneumonia. Thrombosis of pulmonary vessels and/or hemorrhage are potential complications

Table 1 Complete remissions of lymphoma with treatment in 270 of 662 patients (41 %)[a]

	Number of patients[b]
Decreased immunosuppression	169 (52)
Excision	89 (23)
Acyclovir	71 (2)
Chemotherapy	65 (20)
Radiotherapy	46 (14)
Immunotherapy (includes – α-interferon, gamma globulin, monoclonal anti-B cell antibodies, donor T-cell administration)	23 (2)

[a] With or without treatment 277 patients died of cancer and 137 died of other causes, of which infection was a major factor
[b] Figures in parentheses represent complete remissions when a particular treatment was the only therapy given

[9]. The radiographic appearance of *Aspergillus* pneumonia can be highly variable and includes diffuse interstitial disease, diffuse nodularity, and consolidation [5]. Isolated progressive lymphadenopathy is an exceedingly rare presentation. Blood cultures are frequently negative, even with dissemination. Positive sputum or bronchoalveolar lavage (BAL) cultures are suggestive in a high-risk patient, but oropharyngeal colonization and culture contamination is difficult to rule out. A definitive diagnosis still requires histologic confirmation or a positive BAL culture in the relevant clinical setting. Antigen and antibody testing are not yet proven to be of clinical utility [9].

This case illustrates that two disorders, fungal infection and lymphoma, which have widely differing treatments and prognoses, can present in identical fashion clinically. The development of a low-grade fungal infection several weeks after cessation of immunosuppressive therapy probably indicates the persistence of a severely immunosuppressed state. To avoid a serious diagnostic and, possibly, fatal therapeutic error, it is advisable that patients who have ostensible progression of lymphoma, despite apparently successful initial treatment, should have new lesions biopsied and a definitive histologic and/or culture diagnosis made. This case raises the question of whether a few patients, previously reported to the CTTR, who received chemotherapy for progressive lymphoma and who died of infection may have been similar to our patient and had both conditions prior to the initiation of chemotherapy but were inadequately worked up.

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