Pulmonary Sarcoidosis Following Stem Cell Transplantation*

Is It More Than a Chance Occurrence?

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Noninfectious pulmonary complications are one of the major side effects of hematopoetic stem cell transplant (HSCT); however, the development of pulmonary sarcoidosis post-HSCT is uncommon, with only three cases previously reported. In each of those cases, sarcoidosis was also diagnosed in the stem cell donor. We now report four cases of de novo pulmonary sarcoidosis occurring post-HSCT (3 autologous HSCT and 1 allogeneic HSCT). We suggest that pulmonary sarcoidosis may develop following either autologous or allogeneic HSCT, and the prevalence may be 10-fold higher than that of the normal population.

Key words: bone marrow transplant; granuloma; sarcoid; stem cell transplant

Abbreviations: alloHSCT = allogeneic HSCT; autoHSCT = autologous HSCT; HSCT = hematopoetic stem cell transplant

Hematopoetic stem cell transplantation (HSCT) is being used increasingly for the management of malignant and nonmalignant conditions. Pulmonary complications can be seen in 10 to 64% of patients undergoing HSCT, with the incidence seemingly dependent on the specific therapeutic regimen used. In over half these patients, noninfectious pulmonary complications are responsible for significant morbidity and mortality. Noninfectious pneumonitis may present as idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, or delayed pulmonary toxicity syndrome, as well as other drug toxicity related reactions. The development of sarcoidosis post-HSCT is very uncommon, with only three reports suggesting the possible transmission of sarcoidosis from the donor stem cells to the allogeneic HSCT recipient. The paucity of literature on the association of sarcoidosis with HSCT prompted this report.

Here, we present four patients who developed biopsy-proven pulmonary nonnecrotizing epithelioid granulomatous lesions compatible with sarcoidosis following HSCT. Three of the patients were treated for breast cancer with high-dose chemotherapy along with autologous hematopoetic stem cell transplantation (autoHSCT), while the fourth patient received an allogeneic HSCT (alloHSCT) for chronic myeloid leukemia.

CASE REPORTS

Case 1

A 51-year-old woman was diagnosed with chronic myeloid leukemia with a positive Philadelphia chromosome. She was treated with hydroxyurea for 6 months and subsequently was maintained on interferon therapy. Her disease relapsed, and she underwent high-dose cyclophosphamide therapy and total body irradiation, followed by alloHSCT. Post-HSCT, her course was complicated by diffuse alveolar hemorrhage, influenza A pneumonia, and acute graft-vs-host disease requiring high dose steroids and cyclosporin. Six months following HSCT, she developed shortness of breath for a period of 2 weeks and low-grade fever. A chest CT scan showed bilateral ground glass and nodular opacities. Transbronchial biopsies showed nonnecrotizing granulomas consistent with sarcoidosis. She was treated with oral prednisone (40 mg/d for 8 weeks and gradually tapered over the next 4 months) with resolution of both her symptoms and abnormal radiographs.

Case 2

Following 6 months treatment with autoHSCT for recurrent breast cancer, a 50-year-old woman was referred to us for evaluation of miliary lesions seen on chest roentgenogram. The patient gave a history of vague joint pains, fatigue, lethargy, and low-grade fever for the past one month. A CT scan of the chest revealed bilateral hilar lymphadenopathy and diffuse miliary opacities. Transbronchial biopsies revealed nonnecrotizing epithelioid granuloma consistent with sarcoidosis. Flow cytometry of BAL fluid revealed a predominantly polyclonal B-cell lymphocytic population. The patient was treated with oral prednisone (40 mg/d), with symptomatic improvement, normalization of her pulmonary function tests within 5 weeks, and resolution of her miliary opacities. However, the hilar lymphadenopathy persisted.

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Common antigenic triggers. Either, or both, may induce sarcoidosis. First, sarcoidosis is due to one or more environmental inhalational triggers. Second, sarcoidosis is due to an abnormal immunological host response to common antigenic triggers. Either, or both, may induce the expression of monocytic-derived cytokines and chemokines, and/or enhance Th1-type responses, leading to the development of the prototypical microscopic finding in sarcoidosis, the epithelioid granuloma. We speculate that the postHSCT lung environment may promote nonnecrotizing epithelioid granulomatous formation caused by high levels of some of these chemokines including MCP-1, CCR1, CCR2, IL-8, and Rantes. Based on approximately 2,600 HSCTs performed over a 12-year period and 4 cases of sarcoid, we estimate the prevalence of sarcoidosis in the HSCT population to be about 150 cases per 100,000 or about 10-fold higher than that of the normal population.

Clinically, all cases of sarcoidosis had their onset of granulomatous response after complete engraftment of their bone marrow, indicating that a responsive immune system is a prerequisite for the formation of granuloma (Table 1). In the setting of malignancy, the development of mediatinal and/or hilar lymyadenopathy raises concerns of relapsed neoplastic processes and can result in unnecessary distress and further aggressive chemotherapy. In fact, two of our patients were scheduled to receive chemotherapy for “metastatic disease” the week following their bronchoscopy, as they both had hypermetabolic activity on positron emission tomography studies.

In conclusion, pulmonary epithelioid granulomas suggestive of sarcoidosis can develop following HSCT and may be more common than previously thought. Therefore, in the appropriate clinical setting, lung tissue biopsies should be obtained to evaluate for this possibility. Further investigations into the underlying mechanisms of this association may also be helpful in our understanding of the pathogenesis of pulmonary sarcoidosis.

REFERENCES


Table 1—Review of Patient Characteristics of All Reported Cases of Sarcoidosis PostBMT

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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<th>Sundar(\text{**}) 2001</th>
<th>Tauro(\text{**}) 2001</th>
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<td>47</td>
<td>48</td>
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<tr>
<td>Family history of sarcoidosis</td>
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<td>No</td>
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<td>No</td>
<td>Yes(\text{†})</td>
<td>Yes(\text{†})</td>
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<td>3</td>
<td>120</td>
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* BMT = bone marrow transplant; F = female; M = male; C = Caucasian; AA = Afroamerican; Allo = allogeneic; Auto = autologous; TBI = total body irradiation; NHL = non hodgkin’s lymphoma; CML = chronic myeloid leukemia. NK = not known.
† BMT from sibling diagnosed with sarcoidosis.
‡ BMT from sibling who developed sarcoidosis after stem cell harvest.

Case 3

A 47-year-old woman 12 weeks following autoHSCT for advanced-stage breast cancer was referred for evaluation of new hilar and mediatinal lymphadenopathy, with pulmonary nodules noted on chest CT. Transbronchial biopsies revealed nonnecrotizing granuloma consistent with sarcoidosis. She was treated with oral prednisone (60 mg/d), and her intrathoracic lesions resolved completely after 8 weeks. Six months later, when the prednisone was tapered to below 10 mg/d, she developed skin lesions, which resolved completely after 8 weeks. Six months later, when the prednisone was tapered to below 10 mg/d, she developed skin lesions, which resolved completely after 8 weeks.

Case 4

A 48-year-old woman had undergone autoHSCT for recurrent breast cancer and 10 years later was found to have new onset mediatinal adenopathy. Mediastinoscopy showed no evidence for tumor but did find nonnecrotizing granulomas consistent with sarcoidosis. Because she was asymptomatic, no treatment was given, and a 1-year radiographic follow-up was unchanged.

DISCUSSION

Nonnecrotizing granulomas have been associated with infections, inflammatory conditions, and/or drugs, but rarely have they been reported following HSCT. All four of our patients had no evidence for infections (mycobacterium and fungus) based on surgical pathology stains and cultures. A review of the literature has revealed three case reports of patients developing sarcoidosis following allo-HSCT. However, these patients received stem cells from siblings who were each diagnosed with pulmonary sarcoid, suggesting the possibility of a transmissible agent.

There are two major hypotheses concerning the pathogenesis of sarcoidosis. First, sarcoidosis is due to one or more environmental inhalational triggers. Second, sarcoidosis is due to an abnormal immunological host response to common antigenic triggers. Either, or both, may induce the expression of monocytic-derived cytokines and chemokines, and/or enhance Th1-type responses, leading to the development of the prototypical microscopic finding in sarcoidosis, the epithelioid granuloma. We speculate that the postHSCT lung environment may promote nonnecrotizing epithelioid granulomatous formation caused by high levels of some of these chemokines including MCP-1, CCR1, CCR2, IL-8, and Rantes. Based on approximately 2,600 HSCTs performed over a 12-year period and 4 cases of sarcoid, we estimate the prevalence of sarcoidosis in the HSCT population to be about 150 cases per 100,000 or about 10-fold higher than that of the normal population.

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In conclusion, pulmonary epithelioid granulomas suggestive of sarcoidosis can develop following HSCT and may be more common than previously thought. Therefore, in the appropriate clinical setting, lung tissue biopsies should be obtained to evaluate for this possibility. Further investigations into the underlying mechanisms of this association may also be helpful in our understanding of the pathogenesis of pulmonary sarcoidosis.

REFERENCES

We report a complex case of percutaneous intervention on a right coronary artery with calcific stenoses and a large coronary aneurysm with long longitudinal diameter, which was successfully performed using a polytetrafluoroethylene-covered self-expandable stent (Symbiot; Boston Scientific; Natick, MA). The use of this new device may enhance the anatomic indications for percutaneous interventions on coronary aneurysms.

**Key words:** coronary aneurysm; percutaneous coronary intervention; polytetrafluoroethylene-covered stent

**Abbreviation:** PTFE = polytetrafluoroethylene

Coronary atherosclerotic aneurysms are sometimes found during diagnostic coronary angiography in patients with different ischemic syndromes. The availability of polytetrafluoroethylene (PTFE)-covered stents has greatly improved the management of such pathologies, allowing the percutaneous exclusion of the aneurysm in selected cases.

We present the case of a large coronary aneurysm located between two calcific stenoses that was successfully managed percutaneously by using a novel PTFE-covered self-expandable stent (Symbiot; Boston Scientific; Natick, MA) that was designed to reduce distal embolization during interventions on saphenous vein grafts.

**Case Report**

A 77-year-old man, who was dyslipidemic and hypertensive, and had recently experienced an inferior myocardial infarction with an impaired ejection fraction, was referred to our catheterization laboratory for diagnostic coronary angiography. Coronary angiography (Fig 1, left, a) revealed single-vascular coronary disease with a tight, calcific stenosis at the end of the proximal right coronary followed by a large aneurysm involving the whole mid-portion of the vessel (quantitative coronary measurement: length, 33 mm; transversal maximum diameter, 28 mm). In the third segment of the vessel, a moderate calcific stenosis (ie, 50 to 60%) was also present. An elective percutaneous coronary intervention with the aim of dilating the two coronary stenoses and excluding the coronary aneurysm was planned.

After positioning an SF JR4 guiding catheter, a 0.014-inch extra-support floppy PTFE (Choice; Boston Scientific) was placed distally to the diseased portion of the vessel. A second 0.014-inch guidewire (BHW: Guidant; Indianapolis, IN) was positioned parallel to the first as a “buddy wire” to improve the support during the following phases of the procedure. The proximal lesion was dilated first with a 3 × 20-mm balloon and then with a 3.5 × 9-mm balloon. Subsequently, it was decided to try to implant a PTFE-coated self-expandable 4 × 45 mm stent (the Symbiot stent). The advancement of the stent was extremely difficult and only after deep intubation of the guiding catheter was it possible to place the stent distal to the post-aneurysm stenosis. During the deployment, the stent shifted slightly distally, finally leaving the very proximal part of the aneurysm uncovered (Fig 1b). The procedure was then successfully completed by placing a PTFE-covered balloon-expandable 3.5 × 16-mm stent (JOSTENT Graftmaster; Abbott Vascular Devices; Redwood City, CA) to cover the proximal part of the aneurysm and the proximal stenosis, followed by postdilation of the two stents with a 4.5 × 20-mm balloon (final angiographic result shown in Fig 1, right, c).

No troponin T elevation was recorded after the procedure, and the patient was discharged from the hospital the day after the procedure and received medical therapy including aspirin, ticlopidine, and low-dose warfarin. The patient remained free of symptoms until 4 months after the procedure when he was readmitted to the hospital for a follow-up angiogram that revealed the absence of early restenosis and the persistent exclusion of the aneurysm.

**Discussion**

The JOSTENT PTFE-covered balloon-expandable stent has been shown to be an effective device for the percutaneous management of coronary aneurysms. Here we present a case of a successful exclusion of a large coronary aneurysm with a new PTFE-coated self-expandable stent (the Symbiot). This stent, which has been designed to optimize the interventional treatment of saphenous vein grafts, may offer some advan-