

# Inflammatory pseudotumors after stem cell transplantation

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## Abstract

Inflammatory pseudotumors (IPT) are rare tumors that occur in various organs and tissues. The clinical picture varies from the more frequent benign lesions to rare malignant tumors with distant metastases. IPTs associated with hematopoietic stem cell transplantation (HSCT) is rarely reported. In this article, we review the reports of IPT after HSCT. We also review the possible factors involved in the pathogenesis. IPT may be rare but they are a potentially serious complication of HSCT. A knowledge of these entities and insistence on a definitive biopsy of mass lesions in the post-HSCT period can avoid unnecessary treatment such as radical surgery, chemotherapy or radiotherapy.

## Introduction

Inflammatory pseudotumors (IPTs) are rare and usually benign tumors but difficult to distinguish from malignant tumors with diagnostic techniques. They may be asymptomatic or may present with inflammatory or mass-related symptoms and signs.<sup>1</sup> The pathogenesis is still not clear. IPT of different organs associated with hematopoietic stem cell transplantation (HSCT) has been reported in only eight patients to date.<sup>2-8</sup>

## Review of previous literature

Fangusaro *et al.*<sup>2</sup> reported the first cases of IPT after HSCT in two pediatric patients. The first case was a boy aged 8 years with acute lymphocytic leukemia (ALL) who achieved remission after second-line chemotherapy. Following conditioning with high-dose cytosine arabinoside and total body irradiation (TBI), he underwent allogeneic HSCT. The major early complications were acute skin and gut graft *versus* host disease (GVHD). Liver IPT appeared at 28 months, presenting with abdominal distention. After lobectomy with complete resection of the mass, patient remained in good clinical condition postoperatively. The case 2 was a boy aged 3 years with

neuroblastoma. Following conditioning with carboplatin, etoposide, melphalan and TBI, he received an autologous HSCT. He first developed an esophageal stricture due to radiation therapy 2 years afterwards and underwent balloon dilatation. A mass detected within the esophagus 4 months later. After surgical resection, the mass was diagnosed as IPT. The patient remained in good clinical condition postoperatively and had no recurrence.

The case 3 was a 23 year old woman who underwent allogeneic HSCT for ALL.<sup>3</sup> Renal IPT appeared at 10 months, presenting with abdominal distention. Unilateral nephrectomy was performed without complication.

The case 4 was a 50 year old woman who had undergone allogeneic HSCT for acute myeloid leukemia (AML). Conditioning was with 120 mg/kg cyclophosphamide (CY) and total body irradiation (TBI). After 19 months, she had a sensory disturbance that involved the left side of the body. A mass detected on cranial imaging.<sup>4</sup> Tumor was resected but she died from a fungal infection 5 months after IPT diagnosis.

Case 5 was a man aged 42 years who underwent allogeneic HSCT for AML.<sup>5</sup> Conditioning was with 16 mg/kg busulfan and 120 mg/kg CY. The patient had a dyspnea and GVHD at 12 months. Pulmonary imaging showed lung IPT. High-dose steroid treatment provided resolution of both pulmonary and GVHD symptoms.

Case 6 was a 32 year old man. He developed bladder IPT after allogeneic HSCT for AML.<sup>6</sup> Conditioning was with busulfan 4 mg/kg/day, orally on days -7 to -4, and cyclophosphamide (CY) 60 mg/kg/day, i.v. on days -3 and -2. Hyperhydration and mesna (30 mg/kg, four times a day) during CY infusion was given in order to prevent CY-induced hemorrhagic cystitis (HC). The patient experienced dysuria with macroscopic hematuria and clots in the urine on day -1. Urinary system ultrasonography on day +14 revealed a dense echogenic lesion with irregular borders like a clot. Cystoscopy done and a mass of clot was found in the bladder on day +17. After removal of clot, there was no active bleeding. During follow-up, on day +71 a mobile echogenic mass in the bladder detected. Complete transurethral resection (TUR) of the mass was performed. After 2 months later the tumor recurred but smaller than the initial lesion which was treated by TUR, too.

Case 7 was a Japanese woman aged 36 years with chemorefractory adult T-cell leukemia (ATL).<sup>7</sup> There were no human leukocyte antigen-identical sibling donors, and therefore unrelated umbilical cord blood was arranged. Approximately 18 months post transplant, the patient developed a cough, slight fever and malaise. Slight anemia and thrombocytosis also appeared. Computer tomography of the chest revealed a solid mass. The pathologic

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findings appeared to be compatible with IPT. Anti-inflammatory medication improved the clinical symptoms, and the mass lesion exhibited no obvious change, while the ATL remained stable.

Case 8 was a boy aged 10 was diagnosed with B-precursor ALL. He was treated with a regimen of intensive chemotherapy and declared in remission. He was diagnosed with bone marrow relapse two yr later, and after he was treated with a second course of chemotherapy, he was then referred for bone marrow transplantation from an unrelated donor. Then reported slowly developing dyspnea on exertion and cough around seven months post- allogeneic hematopoietic cell transplantation. After 8 months he was diagnosed as having an endobronchial tumor based on imaging, subtotal resection was performed and histology confirmed ALK-positive submucosal spindle-shaped cells with infiltrative cells, compatible with IPT. After this procedure there was no tumor regrowth.<sup>8</sup>

## Discussion

The clinical picture of IPTs are generally varies from the more frequent benign lesions to rare tumors, which are multifocal and prone to recurrence (Table 1).<sup>6-8</sup>

Local and vascular invasions are usually seen. IPTs may rarely undergo malignant transformation, occasionally with distant metastases.<sup>9-11</sup> Coffin *et al.* emphasized their neoplastic nature and proposed the use of the

**Table 1. Inflammatory pseudotumor of different organs in patients following hematopoietic stem cell transplantation.**

Case	Age	Sex	Type of HSCT	Primary disease	Time of IPT after HSCT	Involved organ	Possible factor for IPT	Therapy	Outcome
1	8	M	Allogeneic	ALL	28 months	Liver	CT+TBI+ immunosuppression	Hepatic lobectomy	Alive
2	3	M	Autologous	NBL	2.5 years	Esophagus	CT+TBI	Resection	Alive
3	23	F	Allogeneic	ALL	10 months	Kidney	CT+immunosuppression	Nephrectomy	Alive
4	50	F	Allogeneic	AML	19 months	Brain	CT+immunosuppression	Resection+brain radiation	Died
5	42	M	Allogeneic	AML	12 months	Lung	CT+immunoSuppression+ pulmonary aspergillosis	Partial resection	Alive
6	32	M	Allogeneic	AML	3 months	Bladder	CT+immunosuppression+ hemorrhagic cystitis	Resection	Alive
7	36	F	Allogeneic	ATL	18 months	Lung	CT+TBI+ immunosuppression	Anti-inflammatory medication	Alive
8	10	M	Allogeneic	ALL	7 months	Lung	CT+TBI+ immunosuppression	Partial resection	Alive

F, female; HSCT, hematopoietic stem cell transplantation; M, male; ALL, acute lymphocytic leukemia; NBL, neuroblastoma; AML, acute myeloid leukemia; CT, chemotherapy; TBI, total body irradiation.

term *inflammatory myofibroblastic tumor* rather than *inflammatory pseudotumor*. The pathologic feature of IPTs is a proliferation of spindle cells associated with a variably dense polymorphic infiltrate of mononuclear inflammatory cells (e.g., lymphocytes, plasma cells, histiocytes, and occasional eosinophils).<sup>1,10</sup>

The lung is the most common site for involvement, but lesions may be detected on extra-pulmonary locations. Coffin *et al.* described 84 patients in the largest IPT series to date. But patients from his reports of IPT are not after HSCT. The presenting complaints of patients are fever, weight loss and pain, together with mass related symptoms of an inflammatory process.<sup>1</sup> Thrombocytosis, anemia, elevation of erythrocyte sedimentation rate and polyclonal hypergamma globulinemia. The involvement sites were mostly the abdomen, retroperitoneum and pelvis, followed by head, neck, upper respiratory tract, trunk and extremities. The pathogenesis and relationship to HSCT is still unclear and several factors are implicated.

Infection has been accepted as a factor for IPT development. Hepatitis C virus, human immunodeficiency virus, Epstein Barr virus, bacterial, fungal and mycobacterial infections have been reported to IPT.<sup>1,10</sup>

A reactive process for IPT is suggested.<sup>10</sup> Maybe a result from an unusual response to noninfectious agents such as trauma or surgery.<sup>9-12</sup> Among the IPT cases in the post-HSCT period, the esophageal IPT developed after the stricture in patient 2. Patient 6 developed IPT after a cystoscopy. It will be a reactive process in response to a noninfectious agent.<sup>13-16</sup>

Chemotherapy and radiotherapy are also potential predisposing factors.<sup>10,17-22</sup> Use of CY was mentioned as associated with bladder IPT in the literature.<sup>10-13</sup> All of the patients with IPT after HSCT were given high-dose chemotherapy and some also received TBI.

Immunosuppression and GVHD are the two factors most likely to be associated with IPTs

that develop after HSCT.<sup>2,5</sup> The immunosuppression may be an important factor. With GVHD, chronic stimulation of the cellular immune system might be the major factor.<sup>23,24</sup> Although IPTs are rare tumors, they can have a significant role on patient morbidity after HSCT. They generally have a much better prognosis than a carcinoma.

Increased morbidity may derive from its site in a vital organ or from aggressive treatment given due to a misdiagnosis of malignancy.<sup>1,13</sup> It is difficult to distinguish IPT from malignant tumors with imaging techniques but time of the lesion is a very important data. IPTs occur earlier in the post-transplant period ranging between 3 months and 2.5 years after SCT. Secondary malignancies occur as later transplant complications due to irradiation and anticancer agents, which are diagnosed at a median of 4.6 years.<sup>22-25</sup>

Definitive histologic evaluation of the mass must be done. So we can avoid unnecessary treatment-related complications.

In summary, although IPTs are rare, it will be a serious complication of HSCT and seen in many organs. Unexplained inflammatory symptoms/signs or any mass lesion in the post-HSCT period of a patient must be considered carefully. Definitive histologic evidence is essential in their diagnosis and differentiation from other malignant tumors.

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