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CASE REPORT

Interdigitating Dendritic Cell Sarcoma Following Adult Liver Transplantation: Case Report and Literature Review

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Abstract Interdigitating dendritic cell sarcoma is an extremely rare neoplasm derived from professional antigen presenting cells. We report an unusual case of such a tumor occurring in a 61-year-old woman who had undergone orthotopic liver transplantation for stage IVA2 primary hepatocellular carcinoma with a raised preoperative α-fetoprotein level, followed by tacrolimus-based immunosuppressive therapy. During her subsequent management, the tacrolimus blood levels ranged from 7.9 ng/mL to 16.1 ng/mL. Physical examination revealed bilateral neck and left axillary lymphadenopathy. No evidence of either chronic hepatitis B virus or Epstein-Barr virus could be detected in serum. An excisional biopsy of a right neck lymph node was performed. Microscopically, the normal architecture was diffusely effaced by a proliferation of spindled to ovoid cells arrayed in a fascicular, ill-defined whorled pattern and small lymphocytes were admixed in varying numbers with the tumor cells. Immunohistochemical studies showed that the tumor cells were positive for S100 protein, vimentin and CD68. Based on these findings, the case was diagnosed as an interdigitating dendritic cell sarcoma. The patient unfortunately had no response to 2 cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone), and died of wide spread disease 6 months after the original biopsy. We propose that tacrolimus-based immunosuppression was associated with the development of interdigitating dendritic cell sarcoma after liver transplantation in this case.

Keywords Adult · Differential diagnosis · Epstein-Barr virus · Interdigitating dendritic cell sarcoma · Liver transplantation · Tacrolimus

Abbreviations

DC	Dendritic cells
IDC	Interdigitating dendritic cells
FDC	Follicular dendritic cells
IDCS	Interdigitating dendritic cell sarcoma
EBV	Epstein-Barr virus
HBV	Chronic hepatitis B virus
HCC	Hepatocellular carcinoma
PET	Positron emission tomography
OLT	Orthotopic liver transplantation
CT	Computed tomography
PTLD	Post-transplant lymphoproliferative disorders

Introduction

Dendritic cells (DC), which are antigen presenting cells present in various sites and at different states of activation with no single marker identifying all DC subsets. Myeloid-derived DC comprise Langerhans cells, interdigitating dendritic cells (IDC), dermal/interstitial dendritic cells and plasmacytoid dendritic cells. Stromal-derived DC include follicular dendritic cells (FDC) and fibroblastic reticular cells [1]. IDC are located in the T-cell areas of peripheral lymphoid tissue and are responsible for stimulating resting T cells in the initiation of strong cellular immunity [2–4].

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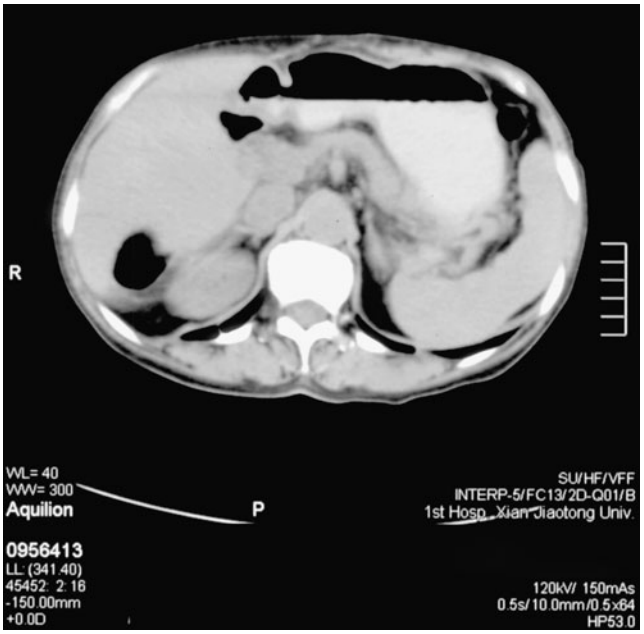

Fig. 1 CT of abdomen, demonstrating mild splenomegaly and no enlarged lymph nodes in the intra-abdominal region

Tumors of IDC origin are extremely rare, with only 54 cases being reported in the English literature. We report here a highly unusual case of a cervical lymph node IDC sarcoma (IDCS) after tacrolimus-based immunosuppression for liver transplantation with a rapidly fatal course, demonstrating no association with Epstein-Barr virus (EBV) infection. To our knowledge, the present report appears to be the first case of lymph node IDCS after liver transplantation (based on the results of a Medline search).

Case Report

Clinical Findings

A 61-year-old woman presented with fever, night sweats and chills in April 2009. Past medical history included chronic hepatitis B virus (HBV)-related liver cirrhosis and primary hepatocellular carcinoma (HCC) in the right liver lobe diagnosed in July 2005, which was found during a routine medical examination. The patient had undergone combination therapy consisting of transarterial chemoembolisation and radiofrequency ablation for HCC, and demonstrated no evidence of extrahepatic spread by a nuclear fluorodeoxyglucose positron emission tomography (PET) scan. Then she underwent orthotopic liver transplantation (OLT) from a 34-year-old deceased donor of accidental death in November 2006, with an increased preoperative α-fetoprotein level (59.75 ng/mL). Pathologic examination showed a solitary, 3.2 cm×3.0 cm×2.0 cm in size, poorly differentiated HCC with portal vein tumor thrombus. Tumor staging was stage IVA2 according to the American Liver Tumor Study Group modified tumor node metastases (pTNM) classification system [5]. The patient had received prednisone, tacrolimus (FK506) and mycophenolic acid (Cellcept) for immunosuppression, and lamivudine for antiviral therapy. Tacrolimus monotherapy was used for maintenance of the immunosuppression. The post-operative blood levels of tacrolimus ranged from 7.9 ng/mL to 16.1 ng/mL.

Physical examination revealed extensive bilateral neck and left axillary lymphadenopathy measuring approximately 0.5–3.5 cm in diameter. Laboratory studies showed mild anemia and thrombocytopenia, with a hematocrit of 30.9% (0.31) and a platelet count of 45×10^9/L, and an elevated lactate dehydrogenase level (328 U/L). Serologic tests against HBV, chronic hepatitis C virus (HCV), EBV and cytomegalovirus were negative, and the serum levels for α-fetoprotein (0.651 ng/mL) and carcinoembryonic antigen (0.477 ng/mL) were normal. Molecular analyses performed on serum by quantitative real-time po1ymerase chain reaction for detecting HBV, cytomegalovirus and EBV DNA were all negative. A chest computed tomography (CT) scan showed no abnormality. Abdominal ultrasonography and CT scans demonstrated mild splenomegaly (Fig. 1). A right cervical lymph node excisional biopsy was performed. Following diagnosis, the patient was found to have involvement of bone marrow. She had no response to 2

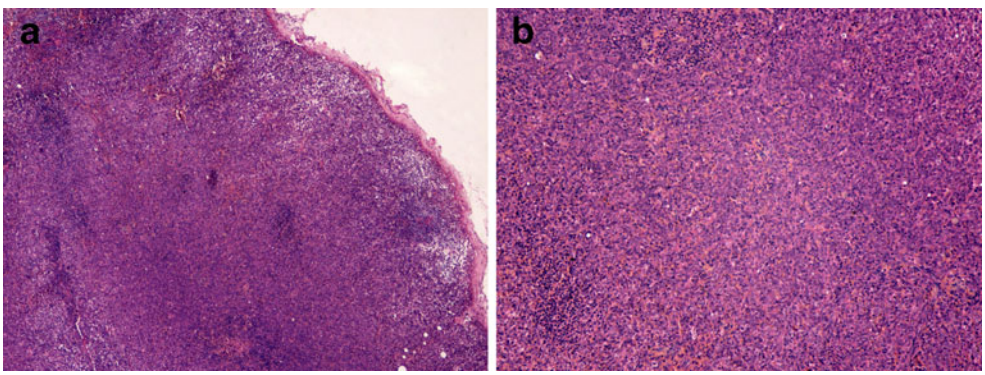

Fig. 2 Lymph node specimen demonstrating diffuse effacement of the normal architecture (hematoxylin-eosin, **a** original magnification 40×; **b** original magnification 100×)

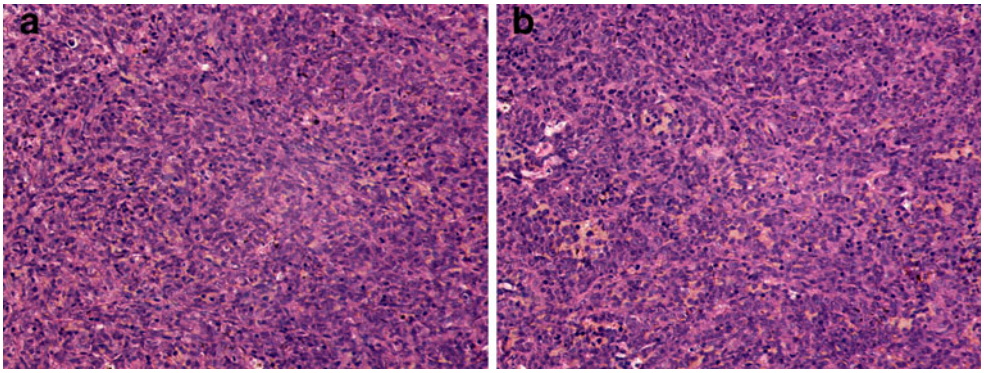

Fig. 3 Spindled to ovoid cells arranged in a fascicular, ill-defined whorled pattern (**a**, **b**, hematoxylin-eosin, original magnification 200×)

cycles of CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone), and died of wide spread disease in October 2006, 6 months after the original biopsy.

Pathological Findings

Grossly, the lymph node measured 0.9 cm×0.7 cm×0.5 cm and the consistency was firm. On cut section, it was vaguely lobulated and tan-white.

Histologically, the lymph node architecture was diffusely effaced by a proliferation of spindled to ovoid cells (Fig. 2a, b), arranged in a fascicular, ill-defined whorled pattern (Fig. 3a, b). The neoplastic cells were uniform and had a moderate amount of slightly eosinophilic cytoplasm, showing indistinct cell borders. The nuclei were oval and indented, with a relatively bland chromatin pattern and inconspicuous nucleoli (Fig. 4a, b, c). Mitotic figures, including atypical mitoses, averaged 6 per 10 high power fields. Marked nuclear pleomorphism or necrosis was not observed. Small lymphocytes were admixed in varying numbers with the neoplastic cells (Fig. 5).

Immunohistochemically, the neoplastic cells were moderately positive for S100 protein in the nucleus and cytoplasm (Fig. 6a). They were also strongly positive for vimentin (Fig. 6b) and moderately positive for CD68 (Fig. 6c) in the cytoplasm. They were negative for CD1a, CD3, CD10, CD20, CD21 (Fig. 6d), CD30, CD35, CD45, CD45RB, CD45RO, CD79α, AE1/AE3, HMB45, epithelial membrane antigen, smooth muscle actin, and desmin. Approximately 15% of the neoplastic cells showed immunoreactivity for MIB-1.

Discussion

In the present case study we analyzed a spindle cell neoplasm arising in the cervical lymph node after liver transplantation that showed morphological and immunohistochemical features of IDCS. To our knowledge, post-transplant IDCS has not been reported until now.

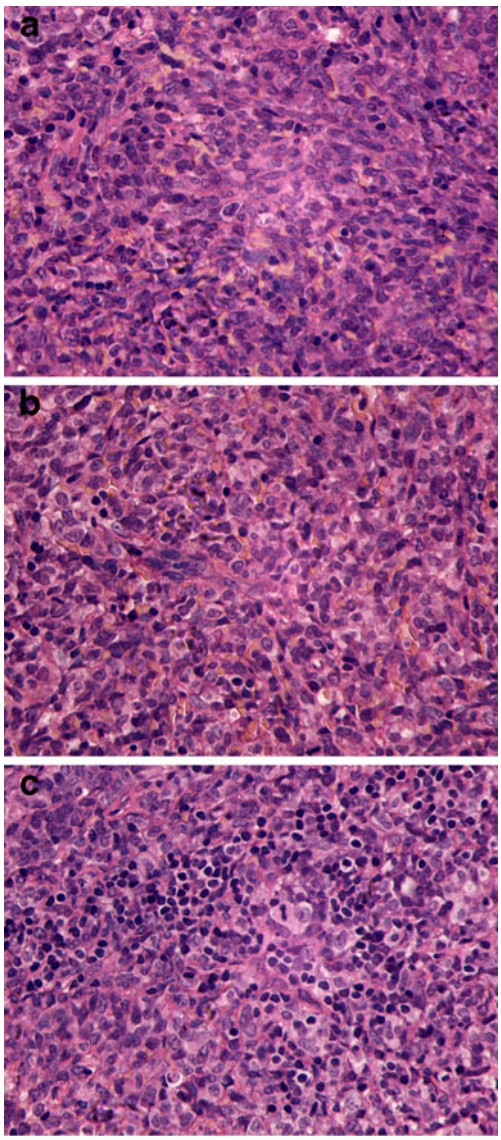

Fig. 4 Tumor cells with indented, vesicular nuclei and indistinct cytoplasmic borders (**a**, **b**, **c**, hematoxylin-eosin, original magnification 400×)

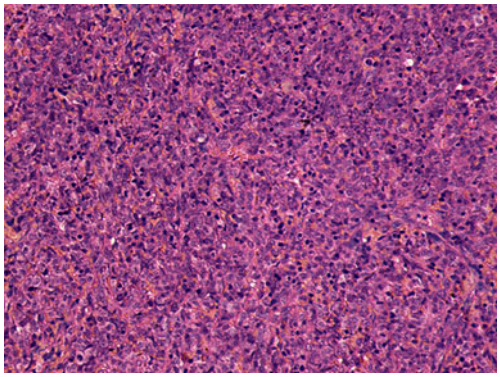

Fig. 5 Scattered small lymphocytes intermingled with the tumor cells (hematoxylin-eosin, original magnification 200×)

IDCS is a rare neoplasm, with a total of 54 cases reported in the English literature, including ours. All cases appear to belong to the IDCS category, with different diagnoses including IDCS, interdigitating reticulum cell sarcoma and histiocytic lymphoma [4, 6–34].

The patients usually present with an asymptomatic mass, and a few have constitutional symptoms such as fever and night sweats, as in our case. The reported cases have a widely affected age range from 2 to 86 years (mean age, 51.2 years), and a slight male predominance (male/female ratio 31:23).

The most common site for IDCS is lymph node. Extranodal primary sites include nasopharynx, tonsil, small intestine, testis, skin and spleen. Involvement has extended to the liver, lung, ovary, skin, bone and bone marrow [4, 6–34]. A history of previous or subsequent carcinoma was reported in four patients [10, 14]. Specifically in our case, the patient had undergone OLT for primary HCC and received immunosuppressive therapy (tacrolimus, Cellcept and prednisone). With the increasing availability of tacrolimus in liver transplantation, there has been concern that this agent may result in an increasing incidence of post-transplant lymphoproliferative disorders (PTLD), especially in young pediatric recipients [35, 36]. Both PTLD and IDCS are tumors of haematopoietic and lymphoid tissues [1], and as no history of relevant donor disease was revealed, we propose that tacrolimus-based immunosuppression is associated with the development of IDCS after liver transplantation.

In the recent series analyzed by Feldman et al [28], 1 case of IDCS was included and showed to be clonally related to a follicular lymphoma, identified in the same lymph node. Chen et al [33] provided the evidence that clonal immunoglobulin receptor gene rearrangements may be detected at a high frequency in sporadic histiocytic/dendritic cell (H/DC) sarcomas. Indeed, these findings suggested that a large subset of these tumors have inherited B-cell genotypes. And the study of Fraser et al [34] demonstrated the clonal transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) into IDCS. These studies provided new insight into the pathogenesis of IDCS. Additionally, no evidence of EBV infection was detected in six reported cases, suggesting that EBV infection may not play an important role in the pathogenesis of IDCS [15, 18, 33].

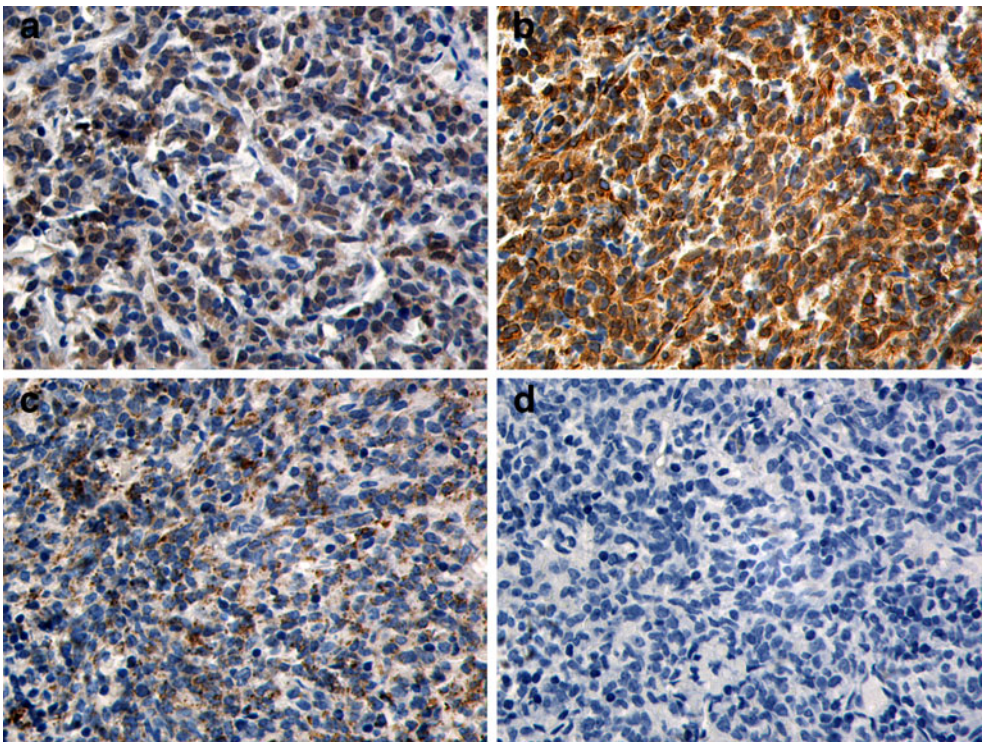

Fig. 6 Immunohistochemical findings (original magnification 400×). **a** Moderate positive for S100 protein in the nucleus and cytoplasm of the neoplastic cells. **b** Diffuse and strong positive for vimentin in the cytoplasm of the neoplastic cells. **c** Moderate positive for CD68 in the cytoplasm of the neoplastic cells. **d** Negative for CD21 of the neoplastic cells

Microscopically, IDCS demonstrates a diffuse proliferation of spindled to ovoid cells with a fascicular, whorled or storiform pattern. Sometimes the histological appearance is indistinguishable from FDC sarcoma. The individual cells may be large and spindled to plump (histiocytoid) with abundant, slightly eosinophilic cytoplasm, ill-defined cell borders and enlarged indented nuclei. Cytologic atypia varies from case to case, although the mitotic rate is usually <5 per 10 high power fields with necrosis being unusual. A characteristic feature is the presence of a variable number of reactive lymphocytes, intermingled with the neoplastic cells, as in our case [1, 13, 14, 19].

Immunohistochemically, there is no specific marker for IDCS, and the tumor cells show a heterogeneous immunophenotype [14]. The cells are consistently positive for S100 protein and vimentin with CD1a and langerin being negative. They are often positive for fascin, CD68, lysozyme and CD45 and negative for markers of FDC (CD21, CD23 and CD35), specific B-cell and T-cell associated antigens, epithelial membrane antigen and cytokeratins [1]. The background small lymphocytes are predominantly CD3+ T-cells with only very few CD20+ B-cells [13, 15]. Ultrastructurally, the cells demonstrate complex interdigitating cell processes. Desmosomes, Birbeck granules and melanosomes are uniformly absent [1, 13, 15].

The differential diagnosis of IDCS has been discussed extensively in previous reports [4, 6–32]. In contrast to IDCS, inflammatory pseudotumour has no morphological atypia or aggressive growth pattern and a polymorphic cell population is usually present [19]. FDC tumors tend to show a more syncytial growth pattern and the nuclei of the tumor cells are more vesicular with peripheral condensation of nuclear chromatin. However, the distinction between tumors of FDC and IDC lineage remains practically impossible on light microscopic appearance alone, and additional adjunctive diagnostic modalities are required. Immunohistochemistry is the most helpful adjunctive test. FDC tumors are positive for the specific markers (CD21, CD23, and CD35) [13]. In addition, diffuse strong clusterin staining is present in FDC tumors in comparison with IDCS [37, 38]. Langerhans cell histiocytosis and Langerhans cell sarcoma express CD1a, langerin and S100 protein, and the ultrastructural hallmark is the cytoplasmic Birbeck granules [1]. Immunostaining for CD30, the associated t(2;5), and other morphologic features can distinguish anaplastic large cell lymphoma from IDCS. True histiocytic tumors are extremely rare. They can be differentiated from IDCS by the histiocyte-like appearance and being negative for S-100 protein [3]. Melanoma is positive for S-100 protein, HMB45 and melanosomes will be seen ultrastructurally [19].

The clinical course of IDCS is generally aggressive, with about one half of patients dying of their disease, a group which our patient unfortunately fell in. The role of chemotherapy and radiotherapy is not clearly defined. Localized disease has been treated successfully with radiation therapy [10]. Most treatment approaches reported for advanced disease have been primarily non-Hodgkin's lymphoma chemotherapeutic regimens, with or without adjuvant radiation [3, 16], but with unpredictable response. Recently, a report of a patient with wide metastatic disease to the liver and abdomen showed complete respondse to 6 cycles of ABVD chemotherapy (adriamycin, bleomycin, vinblastine, dacarbazine) [3, 16]. However, there is no standard therapy for treating this rare and aggressive malignancy.

In conclusion, we have described a case of cervical lymph node IDCS after tacrolimus-based immunosuppression for liver transplantation with a rapidly fatal course, demonstrating no association with EBV infection. Additional more cases of IDCS should be thoroughly studied to further evaluate treatment modalities and outcomes for this rare neoplasm.

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