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CASE REPORT

Neglected Right Hemidiaphragmatic Angle Soft Tissue Shadow in a Renal Transplant Recipient Diagnosed as Lymphoma

Xin R. Li, Ai S. Fu, Jia F. Luo, Hong L. Ji, Cheng X. Nie, Yan L. Ge

Department of Respiratory Medicine, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei Province, China

SUMMARY

Background: **Post-transplant lymphoproliferative disorders are characterized by atypical clinical manifestations, high mortality, and missed diagnosis rates.**
Methods: **We report a case of renal transplantation in a patient with unexplained soft-tissue nodular shadows, and the type of the post-transplant abnormal soft-tissue shadows was clarified by puncture biopsy.**
Results: **The pathologic returns were consistent with the post-transplant lymphoproliferative disease, and the immunohistochemical returns supported a diffuse large B-cell lymphoma (non-growth center origin).**
Conclusions: **In organ transplant patients, when unexplained soft tissue nodular shadows are present, the possibility of post-transplant lymphoproliferative disorders should be considered, and an aggressive puncture biopsy should be performed to clarify the diagnosis.**
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Correspondence:
Yan L. Ge
North China University of Science and Technology Affiliated Hospital
73 Jianshe South Rd
Lubei District, Tangshan, Hebei Province
China
Phone: +86 15932081296
Email: 495732196@qq.com

Ai S. Fu
North China University of Science and Technology Affiliated Hospital
73 Jianshe South Rd
Lubei District, Tangshan, Hebei Province
China
Phone: +86 13393152699
Email: maxfas@163.com

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KEYWORDS

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CASE REPORT

Post-transplant lymphoproliferative disorders (PTLD) are a group of serious and neglected complications occurring after solid organ or bone marrow hematopoietic stem cell transplantations due to immunosuppression caused by long-term use of immunosuppressive agents in the recipients [1]. In recent years, post-transplant lymphoproliferative disorders have become more and more common due to the use of more effective immunosuppressive regimens and the rise in the success rate of transplantations [2]. Diffuse large B cell lymphoma is the most common pathological subtype of monomorphic PTLD [3]. In this article, we report a case of a combined diffuse large B-cell lymphoma 20 years after renal transplantation and analyze its clinical data to improve the understanding of this disease.

The patient is a 62-year-old man, diagnosed with chronic renal failure in the uremic stage 20 years ago, who underwent an allogeneic kidney transplantation, and

who was on long-term immunosuppressant drugs (mertiomaxolide, tacrolimus, and methylprednisolone) after the operation. He was admitted to a local hospital on December 31, 2022, with "intermittent fever for 2 weeks, aggravated by respiratory distress for 3 days." He tested positive for the novel coronavirus antigen and was treated against the novel coronavirus infection. He was admitted to the hospital with a CT as shown in Figure 1B. There was no significant improvement in his condition, so he was transferred to another hospital on January 8, 2023. During the hospitalization, glucocorticoids were given to him to treat novel coronavirus pneumonia, voriconazole antifungal treatment was given, sulfadoxine heparin sodium prophylactic anticoagulation was given, and the tacrolimus and voriconazole blood concentration was monitored dynamically. After the patient's condition stabilized, he was discharged from the hospital on January 25, 2023. A repeat CT on February 9, 2023 (Figure 1C), suggested that he had infectious lesions in both lungs and a soft tissue nodule in the right hemidiaphragmatic angle, which was suspected to be a late residual focus of neocoronary infection. No further treatment was done for the time being. On May 4, 2023, a lung CT (with cough) revealed a nodule in the right diaphragmatic angle area that was significantly larger than before (Figure 1D), and a puncture biopsy was performed to clarify the diagnosis. The pathological examination returned: the nodule is consistent with post-transplant lymphoproliferative disease, the immunohistochemical results support diffuse large B-cell lymphoma (non-growth center origin). Immunohistochemistry: CK7(-), CD3(-), CD79a(+), CD20(+), CD5(-), Ki67(MIB-1) (80% +), EBER(-), CD38 (a few +), HHV-8(-), P53(+), CK(AE1/AE3)(-), Vimentin(+), ALK(lymphoma)(-), CD30(-), CD15(-), EMA(-), CD10 (-), Bcl2(+), Bcl6(+), MUM1(+), c-Myc(+). After diagnosis, 4 courses of chemotherapy were carried out, and now, half a month after the end of his chemotherapy, the patient has no clear complaints of discomfort, and PET/CT was carried out on Sept 27, 2023, to clarify the systemic situation (Figure 1E). The result was considered a complete metabolic remission after lymphoma treatment.

DISCUSSION

We report the case of a patient who was in the recovery period of the novel coronavirus infection when the abnormal right diaphragmatic angle soft tissue nodular shadow was detected in the early stage and was considered to be a residual lesion of the novel coronavirus infection. The diagnosis of PTLD was not considered until the patient's follow-up CT revealed a rapidly increasing soft tissue shadow in the right diaphragmatic angle, and was eventually confirmed by a puncture biopsy. This case was used to analyze the literature on PTLD and to improve clinicians' understanding of the disease. PTLD is recognized as a serious complication occurring after solid organ transplantations. The incidence of PTLD varies according to the transplanted organ, with the highest incidence in combined organ transplants and small bowel transplants and lower incidence in liver and kidney transplants. The reasons for that may relate to the amount of lymphoid tissue in the organ and the intensity and duration of the post-transplant immunosuppression [4]. The present case was a kidney transplantation patient. The pathologic examination return was consistent with the post-transplant lymphoproliferative disease.

The pathogenesis of PTLD is complex and is currently thought to be associated with an EBV infection, an immune suppression, an immunosurveillance deficiency, and a chronic stimulation by graft antigens. EBV infection-associated PTLD accounts for approximately 50% - 70% of the disease [1]. EBV, latent in SOT recipients or of donor origin, is reactivated and infects B-cells when transplant recipients are in a state of immune suppression. Approximately 1/3 of PTLD is not associated with an EBV infection, and the pathogenesis of EBV(-) PTLD differs from that of EBV(+) PTLD, and is similar to that of lymphoma in immunocompetent populations [5,6]. Chronic stimulation with graft antigens has been proposed to contribute to the development of EBV(-) PTLD, but has not yet been demonstrated [7]. There are studies confirming that specific immunosuppressive agents such as cyclosporine, tacrolimus, CD3 monoclonal antibodies, and anti-thymocyte globulin (ATG) have been widely used, all of which have significantly increased the incidence of PTLD [8]. The patient in this case had received a kidney transplantation 20 years ago, and chronic diseases had weakened his body functions. The man was in a state of immunosuppression or even oversuppression of immunity for a long period of time; his body's ability to recognize and remove cancerous cells in a timely manner was insufficient, he was in a state of high risk for infections and tumors, and the use of tacrolimus to inhibit immunity after his renal transplantation carried the risk of increasing the occurrence of disorders or of a proliferation of lymphoid tissues. The PTLD classification is based on the World Health Organization 2017 criteria and describes four main subcategories based on morphological and immunohistochemical features: 1) nondestructive lesions; 2) polymorphic PTLD; 3) monomorphic PTLD (including B-cell type, T-cell type, and natural killer (NK) cell type); 4) typical Hodgkin's lymphoma PTLD. Among them, diffuse large B-cell lymphoma belongs to monomorphic PTLD, which is a common B-cell lymphoma with a highly malignant and aggressive nature and a poor prognosis. The immunohistochemical findings in our patient support diffuse large B-cell lymphoma.

The clinical features of PTLD are usually nonspecific, with symptoms characterized by a disturbed function of the involved organs. Fever, hepatosplenomegaly, lymph node enlargement, and central nervous system symptoms that fail to respond to broad-spectrum antibiotic therapy are the most common, and frequent sites of in-

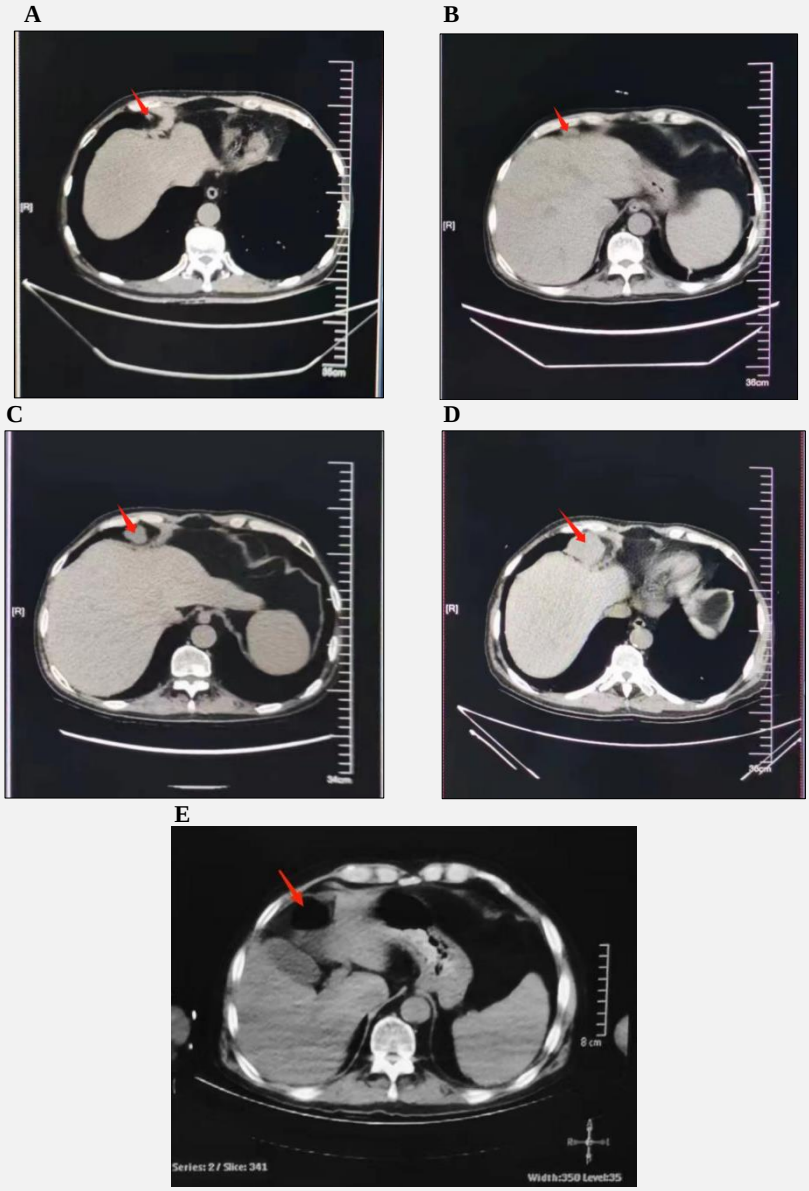

Figure 1. Patient imaging results.

The CT scans of the lungs from August 2022 to May 2023 showed a significantly enlarged soft tissue nodular shadow in the right diaphragmatic angle (Figure 1A - D). The PET/CT on September 27, 2023, showed primary multiple small lymph nodes, none of which had a high radioactivity uptake, no significant change in volume from prior, a complete metabolic remission after treatment for lymphoma was considered, mediastinal 4R, and bilateral hilar small hyperplastic lymph node reactions (Figure 1E).

volvement include the intestines, liver, lungs, kidneys, and bone marrow. Laboratory and imaging tests are nonspecific. Imaging tests can assist in the early detection of lesions, in the assessment of the disease stage, and in the treatment efficacy. The positron emission tomography/computed tomography (PET/CT) has better sensitivity and specificity for PTLD, while MRI can more accurately visualize lesions in CNS than CT [9, 10]. Pathologic examination is the gold standard for confirming the diagnosis, and when PTLD is suspected, PET/CT and a directed biopsy should be performed. Standardized management of organ transplant recipients can effectively reduce the incidence of PTLD and detect PTLD lesions at an early stage. One year after a transplantation is the peak time for PTLD, during which we need to pay close attention to the occurrence of EBV in-

fection and cryptogenic EBV reactivation as well as the clinical manifestations of PTLD in recipients. Most transplant centers in Europe and the United States recommend plasma EBV qRT-PCR every 1 - 2 weeks for 1 year (or at least for several months) after SOT [1,11]. Recipients with PTLD, diagnosed by histopathological biopsy, are recommended to be treated with response-dependent sequential therapy with immunosuppressant tapering, rituximab, and cytotoxic chemotherapy [12, 13]. In recent decades, due to the introduction of a more uniform treatment regimen, improved supportive care, and increased awareness and use of PET/CT for staging and response monitoring, outcomes for patients with PTLD have improved [14].

CONCLUSION

PTLD has a high mortality rate and a poor prognosis. It is easy to misdiagnose and delay treatment due to its clinical symptoms and atypical imaging manifestations. Standardized management of organ transplant recipients, close attention to the occurrence of EBV infection and cryptogenic EBV reactivation as well as clinical manifestations related to PTLD can effectively reduce the incidence of PTLD and improve early detection of PTLD lesions. When abnormal soft tissue nodular shadows appear in organ transplant recipients at an early stage, the diagnosis of PTLD cannot be excluded, and puncture biopsy should be performed as early as possible to clarify the diagnosis. Early and accurate diagnosis of PTLD and a timely and correct treatment can improve the survival rate of patients.

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Ethical Approval:
This study was approved by the Ethics Committee of the North China University of Science and Technology Affiliated Hospital. All procedures performed in the studies were in accordance with the ethical standards. Informed consent was obtained.

Declaration of Interest:
No conflicts of interest.

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