Clinical Presentations and Features of PTLD After HSCT

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In contrast to lymphomas in immune-competent patients, presentation of PTLD in general is associated with a higher number of extranodal involvement and central nervous system invasion. In addition allograft localization is a peculiar finding in solid organ transplantation (SOT)-related PTLD, but seems to be observed less frequently in allogeneic hematopoietic stem cell transplantation (HSCT)-related PTLD. In allogeneic HSCT recipients, risk factors for PTLD development mainly include the degree of HLA matching and, hence, the need for T-cell depletion protocols before transplantation. In addition higher recipient age and underlying primary immunodeficiency disorders are also considered risk factors. PTLD following allogeneic HSCT typically is donor lymphocyte-derived, whereas SOT-related PTLD in most cases is recipient-derived [1].

Presentation of patients with PTLD after allogeneic HSCT may be highly variable due to the organs and structures involved [2, 3]. Often cases are preceded by a mainly asymptomatic phase of EBV reactivation or primary infection in peripheral blood. The lack of symptoms in these early stages may be attributable to the depletion of T cells, preventing typical symptoms of fever and enlarged lymph nodes. However, if left untreated, rapid disease progression finally leading to organ involvement may occur, causing a huge variety of organ-specific symptoms. Late onset PTLD has been described in a minority of patients and almost always results from ongoing immune-suppressive therapy for chronic graft versus host disease (GVHD) [2].

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Based on this concept, there are mainly two forms of clinical presentation: a more classical nodal presentation with frequent involvement of Waldeyer's ring, lymph nodes, liver, and spleen. Patients often present with lymph node, liver, or spleen enlargement or difficulties in swallowing and breathing. Involvement of lung is common and may represent a risk organ, and patients may suffer from gastrointestinal symptoms like abdominal pain, mucocutaneous ulcers, or diarrhea [3–7].

On the other hand patients may present with a fulminant course, resembling primary EBV-mononucleosis infectiosa or even hemophagocytic syndrome with high fevers, cytopenias, and organ dysfunction up to multi-organ failure. The latter is associated with high risk of fatal outcome [8]. Bone marrow examination should be done at least in all patients with blood count abnormalities [9]. A minority of patients (10–15%) presents with involvement of the central nervous system (CNS), which may be suspected in the case of neurological symptoms (headache, seizures, neurologic deficits) [8]. A lumbar puncture and, if symptoms are present, MRI imaging of the brain are advisable in all patients. Recently a new entity, EBV-positive mucocutaneous ulcer, was added to the revised WHO 2016 classification; thus, a thorough inspection of the oral cavity is mandatory in all patients [10].

As symptoms of PTLD are often unspecific, the clinician is challenged by sorting out several differential diagnoses (pathogen-induced sepsis, graft versus host disease, recurrence of the underlying disease, toxic organ failure). A biopsy and histologic evaluation are mandatory whenever deemed possible.

Few studies have compared the clinical presentation of PTLD following allogeneic HSCT and SOT. In a recent retrospective analysis, Romero et al. compared 82 cases of SOT-PTLD with 21 cases of HSCT-PTLD, showing differences in presentation. HSCT-PTLD was associated with a higher incidence of B symptoms and more advanced stage and of specific nodal (Waldeyer's ring), splenic and extranodal (liver and CNS) involvement. In this series 91% of the cases had an early onset presentation [11]. In a large retrospective European Society for Blood and Marrow Transplantation (EBMT) study, extranodal involvement was seen in 42% of the patients [12].

Although most cases of PTLD following allogeneic HSCT are EBV-associated, a recent retrospective analysis of the Center for International Blood and Marrow Transplant Research (CIBMTR) showed 17% of PTLD cases were EBV-negative. Time of occurrence following transplantation, clinical features, and histology were not significantly different between EBV-positive and EBV-negative PTLD. Outcome was poor in both subtypes [13].

In conclusion, clinical presentation of PTLD following allogeneic HSCT may be very variable, often confronting transplant physicians with difficult but important differential diagnoses including several early and life-threatening transplant-related complications. In contrast to SOT-related PTLD, less information is available on clinical presentation, which is probably due to the relative limited number of transplantations (and hence cases) compared to SOT and to the widespread use of preemptive administration of rituximab following allogeneic HSCT.

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