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Clinical and Pathological Review of Post Transplant Lymphoproliferative Disorders

Seema Naik, Hong Zheng, Kevin Rakszawski, Clare Sample, Jeff Sample and Michael Bayerl

Abstract

Posttransplant lymphoproliferative disorder (PTLD) is a rare but potentially serious complication following transplantation with an overall incidence of PTLD of 1–5% in solid organ transplant (SOT) recipients and 1% in hematopoietic stem cell transplant (HSCT) recipients. The clinical and pathological spectrum of PTLD is broad; however, most cases of PTLD occur within the first year after transplantation and are associated with EBV. Clinical features that independently predict rates of response and survival have not been systematically studied for PTLD. Patients whose PTLD expressed CD20 or EBV have shorter intervals to PTLD onset, whereas late-onset cases of PTLD are typically EBV negative. Phenotypic characterization of PTLD reveals potential reliance on EBV or NF-κB signaling instead of B-cell receptor signaling, which links PTLD to other subgroups of EBV-related lymphomas, highlighting new potential treatment approaches. PTLD can be a life-threatening post-HSCT complication due to the impact of the patient’s underlying disease (malignant or nonmalignant) as well as the type and intensity of the conditioning regimen. EBV-negative PTLD is more often a delayed phenomenon post-HSCT compared to EBV-positive PTLD. Further investigations are needed to better understand the role of EBV in the pathogenesis of different forms of PTLD in the immunosuppressed patients.

Keywords: posttransplant lymphoproliferative disorder (PTLD), Epstein-Barr virus (EBV), immunosuppression (IST)
1. Introduction

PTLD is an uncommon complication of hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) with a broad clinical and pathological spectrum ranging from an acute, self-limited illness resembling infectious mononucleosis with histologically innocuous polyclonal lymphoid proliferation to aggressive, life-threatening tumors resembling aggressive lymphomas in immunocompetent individuals. The overall incidence of PTLD is about 1–5% in solid organ transplant (SOT) recipients and 1% in hematopoietic stem cell transplant (HSCT) recipients. Most cases of PTLD occur within the first year after transplantation. Late-onset PTLD, occurring years after transplantation, is often associated with more monoclonal lesions and a worse prognosis [1].

The clinical outcome of untreated aggressive PTLD after HSCT is very poor, suggestive of the biologic heterogeneity between the PTLD and de novo DLBCL. The mortality associated with PTLD induced by EBV infection can be reduced by monitoring EBV by polymerase chain reaction and by preemptively giving rituximab. The prompt initiation of preemptive therapy and early diagnosis of EBV disease are associated with decreased mortality [2, 3].

There is no consensus opinion as to whether a particular subtype of HSCT is associated with increased incidence of PTLD and whether salvage therapy provides survival benefits in patients developing early compared to late PTLD though, empirically, regimens that would reduce EBV-specific T cells, e.g. in vitro or in vivo T-cell purging, are believed to increase the risk of EBV-associated PTLD. Clinical features that independently predict rates of response, progression-free survival, and overall survival have not been systematically studied for PTLD presenting as aggressive non-Hodgkin lymphoma.

From a pathological standpoint, PTLD that represents a spectrum of lymphoid proliferations can be classified as nondestructive, polymorphic, monomorphic, and classical Hodgkin lymphoma types [29] based on morphology, immunophenotype, and clonality. Monomorphic and classical Hodgkin PTLDs are then classified based on their resemblance to de novo lymphomas in immunocompetent individuals, e.g., diffuse large B-cell lymphoma, Burkitt lymphoma, plasmacytoma, plasma myeloma, peripheral T-cell lymphoma, NOS, hepatosplenic T-cell lymphoma, etc. The majority of monomorphic PTLDs resemble aggressive non-Hodgkin lymphoma, and most indolent lymphomas such as low-grade follicular lymphoma and EBV-negative extranodal marginal zone (MALT) lymphoma are not considered PTLD. However, a small number of EBV+ MALT lymphomas have been reported in the post-transplant setting and are considered a bona fide PTLD [29, 30].

2. PTLD in SOT vs. HSCT

Compared to the general population, the SOT patients have a 30–60-fold increased risk of developing PTLD. Most cases of PTLD occur within the first year after transplantation. EBV DNAemia occurs after transplantation in significantly more SOT recipients than HSCT
patients. Correspondingly, more SOT patients also develop PTLD than HSCT patients and also significantly later posttransplant compared to HSCT recipients. The median length of time between transplant and diagnosis of PTLD for SOT patients is 2.8 years versus 121 days for HSCT patients [1, 4].

2.1. PTLD in SOT
In adults, incidence rates range 1–3% in kidney and liver transplants, 1–6% in cardiac transplants, 2–6% in combined heart-lung transplants, 4–10% in lung transplants, and up to 20% in small intestine transplants. The variation in rates among the types of organs transplanted is likely related to the degree and duration of immunosuppression as well as the number of EBV-positive donor lymphocytes in the graft. PTLD is more common in lung and small bowel transplants. Duration of the posttransplant period is important because PTLD is most likely to develop in the first year following transplantation, with an incidence of 224 per 100,000 but falls to 54 per 100,000 in the second year and 31 per 100,000 in the sixth year. PTLD represents a heterogeneous group of non-Hodgkin lymphomas that vary clinically and are ill-defined morphologically [5–8].

2.2. PTLD in HSCT
PTLD develops in approximately 1% of patients post HSCT, among which the majority of cases occur within the first year after allogeneic stem cell transplantation (alloSCT). It is highly related to EBV reactivation. Risk factors that associate with high incidence of EBV-related PTLD include elderly patients (aged ≥50 years at transplantation), T-cell depletion-containing regimens, antithymocyte globulin (ATG) use, and grafts derived from unrelated or HLA-mismatched donors. PTLD can also develop in patients who received autologous stem cell transplants, but the frequency is much lower than alloSCT [9, 10]. PTLD in ASCT cases occurs in younger age group, with shorter duration of onset than solid organ transplantation.

3. Diagnostic markers

3.1. CD20 positivity
The prognostic role of CD20 expression and Epstein–Barr virus (EBV) positivity in PTLD after SOT is poorly understood. In a retrospective study, a total of 45 pediatric SOT patients (28 heart, 11 liver, and 6 kidney) were diagnosed with PTLD 45 months after SOT. Of the 40 evaluable PTLD cases (11 monomorphic, 19 polymorphic, 5 early lesions, and 5 rare subtypes), 32 (80%) had detectable EBV, and 28 (70%) were classified as CD20 (+). Patients whose PTLD expressed CD20 or EBV had shorter intervals between SOT and PTLD onset (28 vs. 64 or 77 months for CD20 and EBV, respectively) (P < 0.02). Patients with CD20 (+) tumors had higher 5-year PTLD-related EFS (83.7% vs. 28.6%, P < 0.001) and OS (95.8% vs. 56.3%, P = 0.01). EBV expression was unrelated to PTLD-related EFS or OS. CD20 expression is thus
found to be associated with timing of development of PTLD and predicts survival in pediatric PTLD in SOT [11].

3.2. Other diagnostic markers

Comprehensive phenotypic characterization of PTLD reveals potential reliance on EBV or NF-kappaB signaling instead of B-cell receptor signaling. Several signaling pathways, cells of origin of PTLD, and their relation to viruses were analyzed by immunohistochemistry and in situ hybridization. Most PTLDs are of activated B-cell origin. Two-thirds of cases show an Epstein-Barr virus (EBV) infection of the neoplastic cells. NF-kappaB signaling components are present in the majority of cases, except for EBV-infected cases with latency type III lacking CD19 and upstream B-cell signaling constituents. Proteins involved in B-cell receptor signaling like Bruton tyrosine kinase are seen only present in a minority of cases. Phosphoinositide 3-kinase (PI3K) is found to be expressed in 94% of cases and the druggable PI3K class 1 catalytic subunit p110 in 76%, while other signal transduction proteins are expressed only in occasional cases. Unsupervised cluster analysis has revealed three distinct subgroups: (i) related to EBV infection, mainly latency type III and lacking CD19, upstream B-cell signaling, and NF-kappaB constituents; (ii) related to EBV infection with expression of the alternative NF-kappaB pathway compound including RelB, CD10, and FOXP1 or MUM1; and (iii) unrelated to virus infection with expression of the classic NF-kappaB pathway compound p65 [12]. EBV and NF-kappaB are important drivers in PTLD in contrast to B-cell receptor signaling. The main signal transduction pathway is related to PI3K. This links PTLD to other subgroups of EBV-related lymphomas, highlighting also new potential treatment approaches [4].

The diagnosis of PTLD relies on comprehensive morphologic examination, immunophenotyping, genetics, and EBV status. Most of PTLDs are of B-cell origin. EBV plays an important role in the pathogenesis of PTLD. The duration of disease onset is shorter in EBV-positive cases.

3.3. EBV viremia and EBV detection by EBER

The majority of EBV infections that occur after transplantation, especially in adults, are clinically silent reactivations. This leads to a subsequent delay in the diagnosis of PTLD. A positive correlation between the degree of EBV DNAemia and the development of PTLD has significant implications for the importance of monitoring viral load after transplantation. In a study done by Holman et al., the risk of PTLD in viremic patients significantly increased with the peak quantity of EBV DNAemia [2, 13]. Since the occurrence of PTLD is significantly related to the viral load, constant monitoring and quantification of EBV-DNA load are utilized as prognostic markers for the development of PTLD. In solid organ transplant (SOT) recipients, approximately 50% of patients develop detectable EBV DNAemia, but only a much smaller subset develops PTLD.

3.4. EBV antigens

The broad EBV latency profile (LMP1+/EBNA 2+) is found to be expressed in 59% of EBV (+) PT-DLBCL and is associated with a more elaborated inflammatory response than intermediate
latency (LMP1+/EBNA 2-) with a role for innate and tolerogenic immune response in EBV + PT-DLBCL. EBV signature is the most important factor in the pathogenesis of EBV (+) PT-DLBCL [14].

3.5. Genomic profiling of PTLD

Clinical, pathological, and molecular genetic characteristics of PTLD show that EBV-positive and EBV-negative PTLDs have distinct gene expression profiling with clustering related to EBV status than immune status. Except for decreased T-cell signaling, EBV-negative PTLDs are inseparable from EBV-negative IC-DLBCL. In contrast, an EBV viral response signature is clearly shown to segregate EBV (+) PT-DLBCL from EBV (−) PT-DLBCL [14, 16].

3.6. PTLD diagnostic algorithm

Systematic morphological, immunophenotypic, and genetic analysis of each PTLD case should be performed. In DLBCL type, one may apply BCL-6, CD10, and MUM-1 immunostains in order to establish the cell of origin according to the Hans algorithm [17]; but the value of this assignment is not well established in this setting. Based on EBV protein expression, the latency type of EBV infection is defined as LMP1-/EBNA2- (type I, restricted), LMP1+/EBNA2- (type II, intermediate), and LMP1+/EBNA2+ (type III, broad). The stromal infiltrate can be estimated semiquantitatively based on the ratio of tumor cells and stromal cells in the entire tissue section. In situ hybridization: EBER (EBV-encoded RNA) in situ hybridization is considered the standard for diagnosis of EBV infection and should be performed in all PTLD cases. PTLD cases are defined as EBV (+) if EBER was expressed in all tumor cells in which RNA was preserved [14].

4. EBV-positive PTLD vs. EBV-negative PTLD

Epstein-Barr virus-positive (EBV (+)) and EBV-negative (EBV (−)) PT-DLBCL have distinct gene expression profiles, and the transcriptomic profile of EBV (−) PT-DLBCL is similar to that of DLBCL in immunocompetent individuals (IC-DLBCL) and supports the hypothesis that EBV (−) PT-DLBCL are de novo lymphomas. EBV (+) and EBV (−) PT-DLBCL have distinct aCGH profiles and shared only one recurrent imbalance. EBV (−) PT-DLBCL, however, display at least ten aberrations recurrent in IC-DLBCL, among which characteristic gain of 3/3q and 18q and loss of 6q23/TNFAIP3 as well as 9p21/CDKN2A. The most prevalent aberration in EBV (+) PT-DLBCL is due to gain/amplification of 9p24.1 targeting PDCD1LG2/PDL2. FOXP1 oncogene and the tumor suppressor CDKN2A implicated in EBV (−) DLBCL do not play a critical role in the pathogenesis of EBV (+) PT-DLBCL [14].

5. Nondestructive vs. monomorphic PTLD

Destructive PTLD, which has typically not correlated with other specific risk factors, has recently been shown to be associated with older recipient age and prolonged receipt of
calcineurin inhibitors. Furthermore, recent data has contributed to and, in some instances, shed light on previous debate concerning the role of viruses other than EBV and the level of HLA mismatch as risk factors for PTLD [15]. Gene association studies focusing on key cytokines and their receptors have identified several polymorphisms that may prove useful to identify patients at risk, with distinction for early nondestructive and late occurring monomorphic PTLD.

6. Monomorphic PTLD vs. polymorphic PTLD

The term PTLD represents a spectrum of B-cell hyperproliferative states that can be classified as nondestructive PTLD, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma, all of which may be associated with Epstein–Barr virus (EBV).

Nondestructive lesions are classified as reactive plasmacytic hyperplasia, florid follicular hyperplasia, and infectious mononucleosis-like PTLD. These lesions are frequently associated with an acute illness similar to mononucleosis, with polyclonal B-cell proliferation, but without evidence of malignant transformation by definition, the lymphoid architecture is preserved.

Polymorphic PTLDs are polyclonal or monoclonal lymphoid infiltrates with evidence of destructive growth patterns including necrosis, destruction of underlying lymphoid architecture, and nuclear atypia. However, polymorphic PTLD does not otherwise meet all criteria for B-cell or T-/NK-cell lymphomas as characterized in immunocompetent patients [1].

Monomorphic PTLDs are monoclonal lymphoid proliferations. Monomorphic PTLD most commonly resembles aggressive B-cell lymphomas such as Burkitt lymphoma/high-grade B-cell lymphoma or diffuse large B-cell lymphoma (DLBCL), as seen in immunocompetent patients. Likewise, classical Hodgkin-like lymphoma variably resembles those observed in immunocompetent patients. Small B-cell lymphomas such as follicular lymphoma, small lymphocytic lymphoma, and EBV-negative marginal zone lymphomas that occur in the post-transplant setting are not characterized as PTLD. A small group of EBV+ MALT lymphoma is now recognized as bona fide PTLD [30].

7. Pediatric PTLD

PTLD occurs more commonly in pediatric patients than in adults. The higher incidence in children is thought to result from being EBV-naïve recipients. PTLDs can arise during post-transplant period after both myeloablative and nonmyeloablative allogeneic hematopoietic cell transplantation. EBV is frequently expressed in PTLD in patients with both HSCT and SOT. Posttransplant lymphoproliferative disorder (PTLD) has been associated with high mortality, but recent anecdotal survival appears better. NAPRTCS registry had 235 registered PTLD cases from 1988 to 2010 which showed that survival has improved with more recent PTLDs in children following kidney transplants [6, 18].
8. Role of immunosuppression (IST)

The degree and duration of immunosuppression play a major role in the development of PTLD. Cytotoxic T cells provide a defense mechanism against EBV-infected B cells in immunocompetent individuals. However, when T-cell function is impaired, this defense mechanism is lost, therefore promoting the development of PTLD.

8.1. ATG and PTLD

In vivo T-cell depletion (TCD) with antithymocyte globulin (ATG) or alemtuzumab (AL) is commonly used in HSCT. TCD facilitates engraftment and reduces the incidence and severity of graft-versus-host disease (GvHD). As reduced intensity conditioning (RIC) and matched unrelated donor transplants (MUD) are now being performed more frequently, ATG and AL have become integral components of preparative regimens. Although ATG and AL provide safer T-cell depletion, delayed T-cell reconstitution following TCD accounts for infectious complications and increased mortality.

EBV PTLD is predominantly derived from donor B cells before reconstitution of the EBV-specific cytotoxic T lymphocyte (CTL) response. It can, however, occur later in the most severely immunocompromised patients with additional risk factors such as donor and recipient mismatch, graft manipulation with T-cell depletion, as well as the degree and duration of immunosuppression.

In a study by Buyck et al., an overall incidence of 6.3% for EBV PTLD was reported in 89 patients with severe aplastic anemia. A marked increase in the incidence (13.3%) was noted in patients exposed to ATG, with 5 of 43 patients developing EBV PTLD [19].

9. Other rare subtypes of PTLD

Although the majority of monomorphic PTLDs fall into the category of diffuse large B-cell lymphoma, other types of lymphoma may also occur. These include plasma cell myeloma, classical Hodgkin lymphoma, or HL-like PTLD, EBV+ MALT lymphoma as well as various T-cell lymphomas with or without EBV infection.

9.1. Burkitt PTLD

A variety of lymphomas can develop as PTLD, although some types appear infrequently and remain poorly understood. PTLD-Burkitt lymphomas behave aggressively and require intensive chemotherapeutic intervention. These display the typical histological features of Burkitt lymphoma but are markedly positive for EBV. While BL-PTLD is a rare entity, it is a discrete form of PTLD with a high EBV expression and should be treated as a high-grade lymphoma. BL-PTLD historically represents a small, but significant, proportion of PTLD cases. BL-PTLD represents 15% of PTLD patients for pediatric heart, lung, and heart-lung transplants from...
1982 to 2009, with a 1.1% overall incidence among pediatric transplant heart-lung recipients, 14% of our pediatric renal PTLD patients, 1.6% among kidney recipients, and 0.71% pediatric liver-transplant recipients, as reported in a single institution study. BL-PTLD is a more aggressive type of PTLD and does not respond to a trial of decreased immunosuppression like P-PTLD and some M-PTLDs. BL-PTLD does require cessation of conventional immunosuppression during treatment with multiagent lymphoma-specific chemotherapy. Bone marrow involvement remains a poor prognostic factor, despite the use of lymphoma-specific chemotherapy in these cases [20–24].

BL after organ transplantation is often found in extra-nodal sites; it involves the central nervous system more frequently than it does in immunocompetent patients. In 70% of BL occurring after organ transplantation, genes or gene products related to EBV can be demonstrated within the tumor cells. The EBV status of the tumor is of important prognostic significance: EBV-positive BL occurring in organ transplant patients usually responds well to reduction or cessation of immunosuppressive therapy; in some cases permanent complete remissions can be achieved even without chemotherapy. In contrast, patients with EBV-negative BL have a very poor prognosis and rarely respond even to aggressive chemotherapy protocols [23].

9.2. T cell PTLD

The etiology of posttransplant T-cell lymphomas remains unclear. Similarities with posttransplant B-cell proliferations are the predominant extranodal presentation and the finding that the time of occurrence is influenced by the type of immunosuppression. In contrast with posttransplant B-cell proliferations, only a minority of the cases are associated with EBV. Most tumors appear to be monoclonal. Prognosis is generally poor, but tumor presentation with localized disease might have a somewhat better prognosis. Ambiguity about the pathogenesis of T-PTLD and the lack of accepted diagnostic criteria may contribute to the rarity and inconsistent characterization of T-PTLD in the literature. While there is a general impression that T-PTLD is very difficult to cure, several recently reported cases demonstrate that these tumors can be very treatment responsive with the use of different chemotherapy regimens than those typically used to treat B-PTLD, such as the intensive ALL-type treatments we employed, and/or the use of different strategies for immunosuppression. Most T-PTLDs are not EBV-driven; thus, reduction of immunosuppression may not be effective as a sole treatment strategy and may be less critical for management of T-PTLD than it is in EBV-driven B-PTLDs.

T-PTLD cases may sometimes exhibit a bimodal response to therapy, with initial eradication of the bulk nodal disease with regimens typically used to treat ALL but persistence of low-level clonal T cells in the marrow, CSF, and lung. Due to small patient numbers, different strategies of treatment may be needed compared to B-lineage PTLD [25, 26].

9.3. HL-PTLD

PTLD that resembles Hodgkin lymphoma (HL-PTLD) has been reported infrequently. These cases have variable numbers of Reed-Sternberg-like (RS-like) cells and highlight differences in the phenotype that may distinguish these from true Hodgkin lymphoma (HD). These
occur 8 months to 13 years following transplant. The large cells of HL-PTLD are pleomorphic B cells that react strongly for CD20 and/or CD79a and express CD30 but are usually negative for CD15 and have few mitoses. They are positive for EBV early RNA (EBER) using an EBER-1 probe, as are some of the background small lymphocytes. HD-PTLD is managed by withdrawal of immunosuppression and variably treated with rituximab to chemotherapy [27]. HL-PTLD and HD appear to be two related but immunophenotypically and biologically distinct forms of lymphoproliferation in posttransplant patients and may require different protocols for their management [27, 28]. Overall survival at 2 and 5 years was 86% with 81% of patients surviving event-free. Rituximab monotherapy has not been shown to lead to long-term remission, but treatment with classical HL chemotherapy is effective and tolerable. New treatment modalities such as CD30-targeted or EBV-specific agents may diminish toxicity.

10. DLBCL vs. PTLD

Within the PT-DLBCL series, EBV (+) cases were different from EBV (−) cases. The fact that all EBV (+) PT-DLBCL cases are of activated B-cell (ABC) origin whereas 45% EBV (−) PT-DLBCL cases were of GCB origin might contribute to the observed difference in survival. Overall, EBV (−) PT-DLBCL was similar to DLBCL arising in immunocompetent individuals regarding median age at diagnosis (63 versus 65 years). The amount of stromal infiltration was significantly higher in IC-DLBCL than PT-DLBCL (12/13 and 12/33 cases contained ≥15% stroma, respectively, P = 0.0012). Geographical necrosis was almost exclusively observed in EBV (+) PT-DLBCL (46%), compared to EBV (−) PT-DLBCL (11%). In contrast, there was no obvious difference in the absolute amount of stromal infiltration between both groups. IDO1 was variably expressed in the tumor and/or stromal cells of 7/22 EBV(+) PT-DLBCL. The Epstein–Barr virus broad latency profile (LMP1+/EBNA2+) was most frequently expressed in PT-DLBCL (n = 13/22; 59%) and associated with a more elaborate inflammatory response than intermediate latency (LMP1+/EBNA2−).

11. Therapy and prevention of PTLD

Prevention of PTLD involves limiting the duration and degree of immunosuppression while still maintaining the adequacy of the donor graft. Achieving a balance of reduction in immunosuppression and preventing graft rejection or graft-versus-host disease can be challenging. Antiviral prophylaxis may also play a role in preventing PTLD, though data are scarce, particularly in SOT recipients. The use of antivirals such as acyclovir, valganciclovir, and ganciclovir is common for HSV, CMV, and EBV prophylaxis, though utilization varies according to institutional guidelines and protocols.

Many transplant centers will preemptively reduce immunosuppression and/or administer the anti-CD20 agent rituximab when EBV reactivation (i.e., ≥1000 EBV genome equivalents per mL) has occurred in the posttransplant setting.
11.1. Treatment of nondestructive lesions

Reduction of immunosuppression is typically recommended for patients with early lesions. If there is residual disease or reduction in immunosuppression is not tolerated or allowable due to concerns regarding the donor graft, rituximab may be utilized.

11.2. Treatment of polymorphic PTLD

A combination of reduction in immunosuppression and rituximab is recommended for patients with polymorphic PTLD.

11.3. Treatment of monomorphic PTLD

For patients with monomorphic PTLD, treatment involves rituximab alone or in combination with systemic chemotherapy, in addition to reduction in immunosuppression. Single-agent rituximab may be utilized in patients with minimal PTLD-related symptoms or low disease burden or if poor performance status or other medical comorbidities preclude the use of systemic chemotherapy. The most commonly employed chemotherapy regimen is R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone); rituximab is omitted in cases of CD20-negative PTLD.

11.4. Conclusion(s)

PTLD can be a life-threatening post-HSCT complication due to the impact of the patient’s underlying disease (malignant or nonmalignant) as well as the type and intensity of the transplant conditioning regimen. EBV-negative PTLD is a delayed phenomenon post-HSCT as compared to EBV-positive PTLD. Biomarkers that measure the extent of immunosuppression may have a role in avoiding PTLD and other posttransplant complications. Further investigations are needed to better understand the role of EBV infection in the pathogenesis of the different forms of PTLD in the immunosuppressed patients.

Author details

Seema Naik*, Hong Zheng1, Kevin Rakszawski1, Clare Sample2, Jeff Sample2 and Michael Bayerl3

*Address all correspondence to: snaik@pennstatehealth.psu.edu

1 Department of Medicine, Division of Hematology/Oncology, Penn State Cancer Institute, Milton S. Hershey Medical Center, Hershey, PA, USA
2 Department of Immunology, Penn State College of Medicine, Milton S. Hershey Medical Center, Hershey, PA, USA
3 Department of Pathology, Penn State College of Medicine, Milton S. Hershey Medical Center, Hershey, PA, USA
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