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Fever in a lung transplant recipient

A 36-year-old woman presented to the emergency department in June 2019 after experiencing high fevers, chills, nausea, decreased oral intake, and diarrhea for 4 days. Her medical history included cystic fibrosis with resultant exocrine insufficiency, and type 2 diabetes mellitus.

In addition, she had received a double lung transplant 9 years earlier, for which she was on a long-term immunosuppressive regimen. The donor had been positive for cytomegalovirus (CMV), whereas the patient had been negative for both CMV and Epstein-Barr virus (EBV). The EBV status of her donor was unavailable. However, the patient's EBV serology was negative when tested 6 months before this presentation, and she was also known to be negative for both hepatitis B and hepatitis C.

She also had a history of stage 3a proteinuric chronic kidney disease with a baseline serum creatinine level of 1.2 mg/dL, hypertension, and an episode of acute transplant rejection in 2014, which resolved with conservative treatment with glucocorticoids. Her home medications were azathioprine, calcium carbonate, cholecalciferol, ferrous sulfate, insulin neutral protamine Hagedorn, insulin aspart with meals, labetalol, a daily multivitamin, prednisone, tacrolimus, ranitidine, and pancreatic enzyme replacement with meals.

She was a lifelong nonsmoker with little alcohol intake, and she said she does not use illicit drugs. She had no recent sick contacts, though she had been hospitalized 4 months earlier for *Pseudomonas aeruginosa* pneumonia, from which she had fully recovered.

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

doi:10.3949/ccjm.87a.19132

INITIAL EVALUATION

Physical examination

On presentation to the emergency department, she was normotensive, febrile with a temperature of 39.5°C (103.1°F), and tachycardic with a heart rate of 133 beats per minute.

Jugular venous pulsation was visible 1 cm above the sternal angle, and respiratory examination revealed fine crackles in the right upper lobe. There was a soft systolic ejection murmur, grade 2 on a scale of 6, heard best at the right upper sternal border.

Her abdomen was nontender on palpation, but her liver could be felt 3 cm below the right costal margin and the spleen at 7 cm below the left costal margin.

Palpation of the head and neck revealed small diffuse lymphadenopathy. The patient also had prominent right axillary and inguinal lymphadenopathy.

A 36-year-old woman presents with high fevers, chills, nausea, decreased oral intake, and diarrhea

Initial investigations

On initial testing (**Table 1**), her serum sodium concentration was 131 mmol/L and her potassium level was 5.6 mmol/L. Her creatinine level was 2.5 mg/dL, up from a baseline of 1.24 mg/dL, consistent with an "acute-on-chronic" kidney injury. She had elevated liver enzymes and bilirubin, as well as neutropenia with an absolute neutrophil count of 0.57×10^9/L.

Urinalysis was negative for nitrites, leukocytes, glucose, bilirubin, and protein, with a nonactive sediment on microscopy.

Liver enzyme analysis revealed the following levels: aspartate aminotransferase 43 U/L, alanine aminotransferase 33 U/L, lactate dehydrogenase 563 U/L, gamma-glutamyl transferase 342 U/L, and alkaline phosphatase 888 U/L.

Ferritin was elevated at 1,983 ng/mL (normal 20–200 ng/mL), and her nonfasting

TABLE 1

The patient's initial laboratory values

Substance	Value[a]	Reference range
Sodium	**131** mmol/L	135–147
Potassium	**5.6** mmol/L	3.5–5.1
Chloride	98 mmol/L	97–106
Carbon dioxide	**17** mmol/L	22–33
Creatinine	**2.5** mg/dL	0.40–1.09
Blood urea nitrogen	**77** mg/dL	5.9–19.9
Corrected calcium	2.41 mmol/L	2.1–2.6
Magnesium	**1.03** mmol/L	0.7–0.96
Bilirubin, total	**1.35** mg/dL	0.29–1.23
Bilirubin, direct	**0.53** mg/dL	0–0.41
Aspartate aminotransferase	**43** U/L	10–32
Alanine aminotransferase	**33** U/L	< 25
Lactate dehydrogenase	**563** U/L	63–200
Gamma glutamyl transferase	**342** U/L	5–29
Alkaline phosphatase	**888** U/L	30–120
White blood cell count	**3.8** × 10^9/L	4.5–11
Absolute neutrophil count	**0.57** × 10^9/L	1.8–5.4
Hemoglobin	**8.8** g/dL	12.0–16.0
Platelets	143 × 10^9/L	140–440
Human chorionic gonadotropin	< 1 mIU/mL	0–5
Random cortisol	20.3 µg/dL	AM 5.1–25.0 PM 2.9–16.0
Tacrolimus level[b]	10.5 ug/L	0–15 ug/L

[a]Abnormal levels are in boldface type.
[b]Level taken on the second day of admission.

triglycerides were minimally elevated at 3.2 mmol/L (< 2 mmol/L). Further results of laboratory testing can be found in **Table 1**.

Chest radiography performed in the emergency department did not show any acute processes.

DIFFERENTIAL DIAGNOSIS

1 Which of the following is the least likely cause of the patient's symptoms?

☐ Hemophagocytic lymphohistiocytosis (HLH)

☐ Bacterial sepsis in an immunocompromised host

☐ Acute viral infection

☐ Posttransplant lymphoproliferative disease (PTLD)

Hemophagocytic lymphohistiocytosis

HLH is primarily a pediatric syndrome, although it can occur in adults in a sporadic fashion, particularly in those with an infectious trigger. It also more commonly arises in older patients (age > 49),[1] whereas our patient was 36.

HLH is characterized by extensive tissue inflammation and destruction, the result of abnormal activation of the immune system. In support of this diagnosis in our patient, HLH has been associated with EBV virus infection as a trigger,[2] and hepatosplenomegaly may be seen.[1] Lactate dehydrogenase is also often quite elevated in HLH,[2] and HLH can be seen in patients with lymphoma, or in those who are immunosuppressed.[3] When cytopenias are seen in HLH, however, they are typically represented by anemia and thrombocytopenia (although any cell line can be depressed).[1–3]

Although our patient had anemia, it was long-standing, and thrombocytopenia was absent. Given the entirety of her presentation, HLH was judged to be less likely than the other possible diagnoses.

Bacterial sepsis

The possibility of bacterial sepsis was strongly considered, as the patient was immunosuppressed, febrile, and tachycardic, and eventually met the diagnostic criteria for febrile neutropenia. In addition, she fulfilled several criteria of the Sequential Organ Failure Assessment, including elevated bilirubin and creatinine,[4] and bacterial sepsis is the most prevalent of all options presented.

Therefore, her neutropenia could have been related to sepsis through marrow suppression, but this was clearly confounded by the multiple immunosuppressive drugs she was taking. Given the known mortality risk associated with sepsis in general—and particularly in a patient on chronic tacrolimus and prednisone—treating this case as bacterial sepsis was the correct first step. However, bacterial sepsis does not explain her new hepatosplenomegaly and lymphadenopathy.

Acute viral infection

An acute EBV or CMV illness could result in high fevers, fatigue, weakness, and hepatosplenomegaly with diffuse lymphadenopathy. Acute CMV and EBV infection or reactivation were strongly considered, given the patient's posttransplant status and symptoms.[5,6] However, while CMV infection can present with acute hepatitis, it does not characteristically present with splenomegaly, which is more typical of a congenital CMV infection.[7]

Regarding other possible viral etiologies, acute viral pneumonia was an initial consideration, given the physical examination findings. However, commonly implicated viruses such as the respiratory syncytial virus, adenovirus, rhinovirus, and influenza[8] do not typically cause splenomegaly.[9]

Additionally, in a posttransplant patient on an immunosuppressive regimen, it is important to consider multiple co-occurring pathologies as the etiologic entity. These include viral or bacterial co-infection, multiple viral co-infection, or viral pneumonia resulting in lung allograft dysfunction,[10] a combination of which could theoretically explain the constellation of findings.

Posttransplant lymphoproliferative disease

PTLD comprises a heterogeneous group of immunosuppression-associated lymphomas that occur after organ transplant.[11] It can present in a variety of ways, often subtly and even as an asymptomatic incidental finding, but occasionally as extensive disseminated disease and even as tumor lysis syndrome.[11,12]

Our patient's main presenting signs and symptoms were nonspecific and included malaise, high fevers, and neutropenia. She had hepatosplenomegaly, which can often be seen with EBV-related PTLD.[11] Further, lactate dehydrogenase is often elevated in patients with PTLD,[13] as was seen here.

Unfortunately, because of the nature of this disease and the fact that it can present in a subtle fashion, PTLD is often a difficult diagnosis to make upon initial evaluation. Certain risk factors, such as older age at presentation, EBV positivity, EBV seronegativity at time of transplant, hepatitis C positivity, as well as type of organ transplant (such as lung and heart) result in increased risk of PTLD.[13–15]

PTLD can develop either early after solid-organ transplant, with approximately 30% of cases being diagnosed within the first year,[16] or in subsequent years posttransplant. The onset of PTLD is thought to be related to the immunosuppressive regimen,[4,16] and it is thought that induction therapy plays a major role in the development of early-onset PTLD. There is some evidence that the use of muromonab-CD3 and antithymocyte globulin may increase the risk of development of PTLD earlier posttransplant.[4,17]

The current understanding of late-onset PTLD is that it is a reflection of the cumulative effect of immunosuppression over time, rather than of a particular immunosuppressant.[4] Therefore, it is important to maintain a high level of suspicion in a transplant recipient with significant immunosuppression, irrespective of time from transplant.

CASE CONTINUED: SPLENOMEGALY, PERSISTENT CYTOPENIAS

The patient was admitted to the hospital and blood and urine cultures were obtained, as well as extensive viral serologic tests. She was empirically treated for presumed bacterial sepsis with piperacillin-tazobactam and vancomycin. She received corticosteroids in stress doses for 1 day, and her prednisone dosing was subsequently increased from 5 mg to 10 mg daily. She received intravenous fluids for her acute kidney injury, and her serum creatinine level declined to its baseline value, consistent with the diagnosis of hypovolemic prerenal acute kidney injury.

The lung donor had been CMV-positive; EBV status unknown

Despite broad-spectrum antibiotics, the patient remained febrile and her neutrophil count continued to decline. Nausea and general malaise continued. Blood cultures and urine culture were negative. Testing of stool for *Clostridioides difficile* was also negative.

Echocardiography showed no valvular vegetation and a normal ejection fraction. Ultrasonography of the abdomen revealed the spleen to be enlarged at 19.2 cm with diffuse retroperitoneal and porta hepatis lymphadenopathy.

At this time, due to ongoing cytopenias, fevers, and in particular, posttransplant status, we strongly suspected PTLD. Thus, serologic

tests for EBV, CMV, human T-cell lymphotropic virus (HTLV), and human immunodeficiency virus (HIV) were sent, and hepatitis B and hepatitis C serologies repeated. The patient's azathioprine and tacrolimus were held, and a dose of basiliximab 20 mg intravenously was given subsequently in an attempt to prevent a recurrent episode of acute rejection in the setting of cytopenias and acute kidney injury.[18]

FURTHER INVESTIGATION AND MANAGEMENT

2 Once acute bacterial infectious causes are reasonably accounted for, what is the best next step in the management and diagnosis of this patient?

- ☐ EBV and CMV serology
- ☐ Addition of antifungal therapy
- ☐ Splenic biopsy
- ☐ Long-term antimicrobial therapy
- ☐ Bone marrow biopsy

Serology in the immunocompromised

Ordering EBV and CMV serology is the correct next step and should include both immunoglobulin G (IgG) and immunoglobulin M (IgM) tests.

The patient was empirically treated for presumed bacterial sepsis, but she remained febrile

Although CMV serology has long been demonstrated to be of little utility in these patients,[19] this is not necessarily true of EBV serology.[20] IgG and IgM against EBV viral capsid antigen (VCA) can be used to preliminarily diagnose acute vs prior infection, although polymerase chain reaction confirmation is still recommended.[20] Acute infection with either CMV or EBV can result in a sepsis-like syndrome, but EBV infection or reactivation is closely related to the development of PTLD, and as such, the case described provides an intriguing illustration regarding the pathophysiology of this association in real time.

In a general sense, EBV-associated malignancies are a well-studied phenomenon, dating back to the discovery of the virus itself in Burkitt lymphoma patients through excisional node biopsies by Drs. Burkitt, Epstein, and Barr in their seminal 1964 article.[21] However, it took until the late 1960s for EBV's role in PTLD to be formally documented, and until 1969 for Penn et al to recognize a pattern and compile a small series of seemingly related cases.[22–24]

Since this time, the understanding of this disease process as being purely EBV-mediated has shifted and changed as knowledge has grown and immunosuppressive regimens have changed. This being said, EBV-positive disease still composes the backbone of the understanding of PTLD pathophysiology, and positive EBV IgM serology can clinch this diagnosis in the right clinical setting. Further detail on this phenomenon can be found below.

Other possible steps

Although it would not be unreasonable to consider adding antifungal therapy in this case, local practice as well as North American guidelines recommend empiric antifungal therapy only in a patient who remains febrile despite 7 days of broad-spectrum antibacterial therapy, whose neutrophil nadir is not expected to resolve by this time, and when the patient is known to be colonized by fungi.[25–27]

Long-term antibacterial therapy is not indicated here, as we had not identified an infectious nidus. Thus, further investigation would be warranted before committing this patient to long-term antimicrobial therapy and its possible adverse effects.

A splenic biopsy would be wrong in this case because this test is much more invasive than the others listed and would be unlikely to yield a diagnostic answer.

THE ROLE OF EBV IN PTLD

3 What is the significance of EBV in PTLD?

- ☐ EBV is the causative agent behind all cases of PTLD
- ☐ EBV causes PTLD only in solid organ transplant recipients
- ☐ Tacrolimus reactivates EBV, which results in PTLD
- ☐ EBV can evade immune detection in the immunosuppressed by incorporating itself into B cells and transforming them

EBV: Cause and effect

EBV can evade immune detection in the immunosuppressed by incorporating itself into B cells and transforming them. The best un-

derstood model of the development of EBV-associated malignancy involves differential expression of surface antigens expressed on host B cells, which is the hematologic cell line most typically affected.[28] These antigens characterize the malignancies they can potentially cause into the subtypes I through III, each progressively more immunogenic than the one prior. EBV-related PTLD is represented by subtype III,[8] because EBV-infected host B cells express a large range of antigens such as LMP1, LMP2, RFO, EBNA1, EBNA2, EBNA3a,b,c, and LP.[29] Consequently, these cells remain quite immunogenic when present in the immunocompetent host by cytotoxic T-cell–mediated immunity and do not lead to the pathophysiology seen in PTLD.[29] This issue becomes important when a person becomes immunosuppressed, however, and it plays a major role in B-cell immune evasion which subsequently sows the seeds for PTLD to proceed unchecked.[15] EBV-positive PTLD is classified as a type III EBV-associated malignancy by the aforementioned schema, based on the surface antigens and immunogenicity of the resultant B-cell.

EBV-negative PTLD

While EBV was initially hypothesized as the driver behind all cases of PTLD, the proportion of EBV-positive PTLD has more recently been evaluated to be approximately 50% when contemporary data were examined, with cases of EBV-negative PTLD growing in proportion in recent decades.[16] Thus, all cases of PTLD are not caused by EBV.

PTLD by transplant type

Although the relative risk of PTLD in lung-transplant recipients is reportedly as high as 58.6—in keeping with one of the highest rates of PTLD outside of multiorgan transplant recipients at 3.0% to 10.0%—there have been many documented cases of PTLD in those receiving bone-marrow transplants.[11,17] Thus, EBV does not cause PTLD *only* in solid-organ transplant recipients.

The role of tacrolimus

Tacrolimus has been implicated as one of the causative agents of EBV-negative PTLD.[16] The proportion of EBV-negative disease has grown in recent decades, and it is generally hypothesized to be related to the transition from cyclosporine to tacrolimus and from azathioprine to mycophenolate as immunosuppressive agents for single-organ transplant recipients.

Tacrolimus has been demonstrated to increase the risk of PTLD,[17] although the same studies that demonstrated this finding also had a greater proportion of EBV-negative patients on tacrolimus, which somewhat clouds this signal. Despite these possible differences, there doesn't seem to be any difference when it comes to outcomes or mortality between EBV-associated and nonassociated disease.[16] Thus, although tacrolimus may play some role in PTLD itself, it has not been shown to "reactivate EBV."

DEFINITIVE MANAGEMENT

4 What is the initial management of PTLD?

- ☐ Reduction in immunosuppression
- ☐ Rituximab alone
- ☐ Combination drug regimen
- ☐ Immunotherapy

Reduction in immunosuppression

Reduction in immunosuppression is correct. Initial management of PTLD is to hold or largely reduce the immunosuppressive regimen.[11,30] Preferably this includes reducing the calcineurin inhibitor by at least 50% and completely discontinuing the antimetabolite.[11] The rationale for reducing immunosuppression is that the immune system may be able to recover functionality of cytotoxic T cells and thus be able to fend off the EBV-infected self-cells.[30] Unfortunately, while this step makes intuitive sense for PTLD management, there is a clear risk to patients in the form of organ transplant rejection.[31]

Her azathioprine and tacrolimus were held, and basiliximab was given

The role of chemotherapy

As a monotherapy, rituximab has demonstrated significant benefit with regard to PTLD management.[11,32] On its own it has induced remission for patients[32] and is often the next step when response to reduction in immunosuppression is suboptimal, or immunosuppression cannot be tapered due to high risk of rejection.[11]

Despite the success of single-agent ritux-

imab therapy, the most commonly used regimen is the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[11,33,34] Treatment depends largely on the histology of the lymphoma and whether it is monomorphic or polymorphic PTLD. In addition, the EBV status of each patient is paramount in determining the optimal treatment type and duration.[11,33] Thus, rituximab or R-CHOP would not be the initial management for most patients with PTLD.

Immunotherapy

While immunotherapy is promising in that it may eventually be used to treat patients with PTLD without requiring reduction in immunosuppression, it is still a developing treatment and would not yet be considered first-line therapy.[11,31]

CASE CONCLUSION

Returning to the case, our patient's EBV anti-VCA IgG and IgM as well as CMV IgG and IgM were both subsequently found to be positive, while her HTLV 1+2, HIV, and hepatitis B and C serology were found to be negative. Her CMV positivity was presumed to be secondary to nonspecific binding during the assay, and this was corroborated by the finding of no detectable CMV DNA on nucleic acid amplification testing.[15] This is a common and understood phenomenon with viral serology, particularly in transplant recipients and the immune-compromised.[19]

Fine needle aspiration and core biopsy of the right axillary and inguinal lymph nodes was done under ultrasonographic guidance

The hematology service was consulted and recommended a bone marrow biopsy, which was performed on the fifth day of admission. Fine needle aspiration and core biopsy of the right axillary and inguinal lymph nodes were performed on the same day under ultrasonographic guidance.

Preliminary results of the bone marrow biopsy as well as the fine needle aspiration demonstrated findings consistent with a B-cell lymphoma. The results from the fine needle aspiration showed 94% lymphocytes, of which 62% were T cells and 1% natural killer cells. There was a significant monoclonal plasma-cell vs a B-cell population, and this was interpreted as either a B-cell lymphoma undergoing plasma-cell transformation or a plasma-cell neoplasm. There was no evidence of a hemophagocytic process.

In the right axillary node, plasma cells and B cells were MUM1-positive, and plasma cells took up the CD138 stain. CD30 staining showed scattered groups of atypical lymphocytes. All of the lymphocytes were positive for CD45. Plasma cells and immunoblasts were positive for lambda light chain restriction with diffusely positive Epstein-Barr virus-encoded small RNAs (EBV in situ hybridization).

These results were definitive for PTLD. Given the consistency with this diagnosis, further nucleic acid testing for EBV was not sought, as the primary management for PTLD (as outlined above), does not involve treatment of this viral reactivation. Despite the aforementioned concerns with viral serology, we believe this to be consistent with EBV reactivation leading to PTLD, especially given the high sensitivity and specificity of anti-VCA serology compared with older methods of viral serologic testing, but optimally PCR would have clinched this diagnosis beyond a reasonable doubt.[20]

Other donor-derived infectious diseases (aside from the already ruled-out hepatitis B, hepatitis C, HIV, and HTLV) were thought to be less likely with the given presentation and timeline. These include less-common pathogens such as lymphocytic choriomeningitis virus, rabies, and *Mycobacterium tuberculosis*.[35]

The patient was subsequently transferred to a quaternary care hospital possessing a dedicated medical unit staffed by lung transplantation physicians. Computed tomography of the chest, abdomen, and pelvis was performed there and found widely disseminated lymphadenopathy in the chest, neck, and abdomen. Thus, the Ann Arbor stage was IV. The patient has thus far received 2 cycles of R-CHOP and is recovering from her acute illness.

SALIENT POINTS

It is important to remain suspicious of PTLD when solid-organ transplant recipients present with subtle findings. Making the connection between elevated LDH, cytopenias, and constitutional symptoms in patients who have undergone solid organ transplantation is essential in the diagnosis of PTLD.

Further, it is important to thoroughly examine the patient for lymphadenopathy and

organomegaly and to pursue appropriate imaging studies and biopsy for patients in whom you suspect this diagnosis.

EBV serology and PCR are essential in understanding how the patient developed PTLD and in dictating further treatment.

The first step in treatment is still to reduce immunosuppression and maintain a high clinical suspicion for PTLD in patients presenting post solid organ transplantation, as well as to involve respective medical subspecialties early, particularly hematology.

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