A 62-year-old man with acute myeloid leukemia, evolved from myelodysplastic syndrome after allogeneic bone marrow transplant, was admitted to the hospital because of worsening fatigue and altered level of consciousness. On arrival at the hospital, the patient was markedly fatigued and had signs of encephalopathy. He reported no fevers, chills, or diaphoresis but noted new urinary incontinence and nausea. His medical history was notable for a matched unrelated donor allogeneic hematopoietic stem cell transplant (HCT), performed 35 days previously, as well as hypertension and peripheral vascular disease. His outpatient medication list included acyclovir, budesonide, dapsone, fluconazole, lisinopril, metoprolol tartrate, omeprazole, oxycodone, sucralfate, tacrolimus, and ursodiol.

Previous therapies for his acute myeloid leukemia included induction chemotherapy with idarubicin and cytarabine, as well as azacitidine consolidation. The patient’s recent HCT history included a preparative regimen of chemotherapy before transplant, 2 doses of antithymocyte globulin in conjunction with subsequent routine prophylaxis for graft-vs-host disease, and continued immunosuppression. Tacrolimus, methotrexate, and filgrastim were administered posttransplant.

The matched donor was a 28-year-old man who was cytomegalovirus (CMV) negative, and the recipient patient’s status was CMV positive. The recipient’s Epstein-Barr virus (EBV) status was positive. He was discharged home on posttransplant day 15 with acceptable graft function. On posttransplant day 28, the patient was hospitalized for nausea, vomiting, diarrhea, and dehydration. Upper endoscopy revealed erythematous gastric mucosa, with mildly increased apoptotic activity in the duodenal biopsies, grade 1/4, negative for CMV staining, suggestive of mild graft-vs-host disease. He was discharged after a 3-day hospitalization and resolution of symptoms.

1. Which one of the following is the most serious CMV-related complication for this patient following bone marrow transplant?
   a. CMV pneumonitis
   b. CMV hepatitis
   c. CMV colitis
   d. CMV retinitis
   e. Guillain-Barré syndrome

Preventing viral infections in HCT recipients is a critical consideration because viral morbidity and mortality are high in this immunocompromised population. There is substantial risk of CMV reactivation in HCT patients, and the safest match consists of a CMV-negative donor with a CMV-negative recipient. Such matches are often not possible, and HLA antigen matching takes precedent over CMV status. The risk of CMV reactivation is highest for CMV-seropositive recipients with a CMV-seronegative donor, but CMV-seronegative recipients who receive allografts from CMV-seropositive donors also require prophylaxis. Primary prophylaxis may consist of therapy with antiviral medications such as ganciclovir, but such medications may pose additional risks such as myelosuppression and thus are reserved only for high-risk cases.

Asymptomatic CMV viremia, as evidenced by persistent or increasing CMV viral load, is common after transplant. Numerous organs can also be involved in CMV infection, but CMV pneumonitis/pneumonia after transplant is the most serious infection. Symptoms include fever, hypoxia, nonproductive cough, and interstitial infiltrates on chest radiography. Mortality is frequently greater than 50%.

See end of article for correct answers to questions.

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Cytomegalovirus hepatitis does occur but is rare and usually manifests as subclinical transaminitis. Gastrointestinal involvement, such as colitis, is the second most common complication and can involve any aspect of the gastrointestinal tract. Gastrointestinal CMV findings can often be confused with graft-vs-host disease. Cytomegalovirus retinitis is uncommon after bone marrow transplant. Guillain-Barré syndrome has been described after CMV encephalitis, but a pathophysiologic link between the two remains unclear.2

Vital signs on current hospital admission were as follows: temperature, 37.0°C; heart rate, 80 beats/min; blood pressure, 144/88 mm Hg; respiratory rate, 32 breaths/min; and peripheral capillary oxygen saturation, 97% while the patient breathed room air. On physical examination, the patient appeared fatigued but was oriented to person, place, and time, although speech at times trailed off and became incomprehensible, requiring frequent arousal. Findings on cardiovascular, pulmonary, and abdominal examinations were within normal limits. Cervical lymphadenopathy was noted. Laboratory studies revealed the following (reference ranges provided parenthetically): hemoglobin, 9.6 g/dL (15.0-22.0 g/dL); white blood cell (WBC) count, 9.3 × 10⁹/L (3.5-10.5 × 10⁹/L); platelet count, 38 × 10⁹/L (150-450 × 10⁹/L); and neutrophils, 6.81 × 10⁹/L (1.70-7.00 × 10⁹/L). A comprehensive metabolic panel was notable for an increased creatinine concentration of 1.5 mg/dL (0.8-1.3 mg/dL), with an estimated glomerular filtration rate of 47 mL/min (>60 mL/min). Aspartate aminotransferase and alanine aminotransferase levels were within normal limits. The lactate dehydrogenase (LDH) value was elevated at 513 U/L (122-222 U/L), and urinalysis yielded no abnormalities. A serum lactate level was not obtained at the time of admission.

2. Which one of the following diagnostic tests is most appropriate in evaluating the patient’s altered level of consciousness?
   a. Magnetic resonance imaging of the brain
   b. Flow cytometry of peripheral blood
   c. Computed tomography of the head followed by lumbar puncture
   d. Crystalloid fluid bolus challenge (30 mL/kg)
   e. Electroencephalography

In immunosuppressed patients, infectious etiologies are high on the differential diagnosis as a cause of encephalopathy. Symptoms such as incoherent speech and altered level of consciousness are concerning for an infection of the central nervous system. Magnetic resonance imaging of the brain could be useful in ruling out masses or structural abnormalities, but it is time-consuming and therefore may be considered after life-threatening infection is ruled out. Flow cytometry of the blood could help evaluate for clonal populations in the patient’s blood cell lines but would not be of immediate utility in a work-up for encephalopathy.

Computed tomography of the head performed before lumbar puncture would help rule out intracranial hemorrhage in the setting of thrombocytopenia, as well as identify potential contraindications to lumbar puncture. A lumbar puncture would permit rapid diagnosis of central nervous system infection, including bacterial meningitis, and help guide antimicrobial therapy, if indicated. Furthermore, malignant involvement of the cerebrospinal fluid (CSF) by cytology may be detected on the collected sample. Intravenous fluid resuscitation is helpful in patients with sepsis, but our patient is afebrile, has no evidence of tachycardia or hypotension, and does not require fluids at this time. Electroencephalography could rule out underlying seizure or epileptiform activity as a cause of the patient’s encephalopathy, but seizure is less likely given his clinical presentation and lack of other neurologic deficits.

Lumbar puncture was performed, and CSF analysis was notable only for an increased protein level of 53 mg/dL (0-35 mg/dL), with no cytological evidence of malignancy. Further infectious work-up did not reveal evidence of bacterial or fungal infection.

3. Which one of the following vaccines would be contraindicated posttransplant during later follow-up in this patient?
   a. 13-Valent pneumococcal conjugate vaccine
   b. Haemophilus influenzae type b conjugate vaccine
   c. Inactivated influenza vaccine
   d. Tetanus, diphtheria, and pertussis vaccine
   e. Herpes zoster vaccine
Recipients of allogeneic HCT are at increased risk of infection, with immunosuppression occurring due to conditioning regimens before transplant, graft function after transplant, and ongoing immunosuppressive drugs given to prevent rejection. Guidelines for preventing infectious complications after HCT were published in 2009.3

The 13-valent pneumococcal conjugate vaccine is more immunogenic than the 23-valent polysaccharide pneumococcal vaccine and is recommended as a 3-dose series starting 3 to 6 months after transplant. Similarly, the Haemophilus influenzae type b conjugate vaccine is well tolerated in these patients and is recommended for 3 doses 3 to 6 months after transplant. An annual inactivated influenza vaccine is recommended for patients 6 months after transplant, but the live attenuated (intranasal) formulation should not be given to HCT recipients. Tetanus, diphtheria, and pertussis vaccine is given 6 months after transplant, with 3 doses administered 1 to 3 months apart. Contraindicated vaccines include most live virus vaccines, such as the herpes zoster vaccine.

The patient underwent fine-needle aspiration of a lymph node in the right side of the neck with core biopsy. Results were positive for a monomorphic B-cell posttransplant lymphoproliferative disorder (PTLD). The vast majority of typical large lymphoid cells were positive for CD20 (B cell), with a few background scattered CD3-positive (T cell) cells present. The features of the biopsy specimen fulfilled the criteria for a diffuse large B-cell lymphoma in the setting of PTLD. On hospital day 2, the patient received one cycle of rituximab, a monoclonal antibody against CD20, for his PTLD. On quantitative DNA testing after rituximab administration, the Epstein-Barr virus level had decreased from 342,000 copies/mL to less than 2000 copies/mL. His tacrolimus dose was reduced and later discontinued during hospitalization.

On hospital day 3, the patient was febrile (temperature, 38.7°C), and progressive tachypnea developed. Laboratory studies revealed an elevated serum lactate level of 6.9 mmol/L (0.6-2.3 mmol/L), elevated anion gap metabolic acidosis, acute renal injury with creatinine level increased to 2.0 mg/dL, elevated troponin value, and elevated N-terminal pro-B-type natriuretic peptide level. He was transferred to the intensive care unit (ICU) because of concern about the tachypnea at more than 30 breaths/min, as well as new-onset lactic acidosis. Multiple cultures of blood, urine, and CSF specimens, as well as imaging studies, failed to identify any infectious etiology beyond the resolved EBV viral levels, which could explain his clinical decline.

The patient’s lactate level continued to rise incrementally, to a value of 8.5 mmol/L on hospital day 6. The serum lactate elevation did not resolve despite resuscitative measures in the ICU, including intravenous fluids, empiric antimicrobials, and optimization of hemodynamics. Metabolic acidosis persisted, with an anion gap of 38 mEq/L (3-11 mEq/L). The LDH level and WBC count (with neutrophilic predominance) continued to increase as well. The patient and his family elected to change his code status to “do not resuscitate/do not intubate.” A mild demand ischemia was noted in the form of mild troponin elevation, but the patient did not have major sequelae of cardiogenic shock, nor did he have features of end-organ hypoperfusion.

4. Of the following, which one is the most plausible etiology for this patient’s increasing serum lactate level?
   a. Tumor metabolism
   b. Bowel ischemia
   c. Tumor lysis syndrome
   d. Failure of lactate clearance
   e. Undiagnosed seizure

An elevated serum lactate level (typically defined as >2.5 mmol/L) can have numerous etiologies.4 There are many possible causes of elevated lactate values in patients with cancer, and indeed, many are multifactorial. However, rapidly proliferating malignancy itself can cause high serum lactate levels. This process is most often recognized in lymphoma or leukemia, when malignant cells shift their metabolic mechanism toward lactate production, even under aerobic conditions. This process is referred to as the Warburg effect. The Warburg effect is thought to be an adaptive mechanism of tumor biology to feed rapid proliferation.

Regional ischemia, such as bowel ischemia, can lead to an elevated lactate level, but this patient has no clinical or radiologic
signs that point toward this diagnosis. Tumor lysis syndrome is associated with elevations in LDH values but not necessarily with increased serum lactate levels. Failures of lactate clearance, such as hepatic dysfunction, can cause elevated lactate levels even in the absence of other causes; however, our patient has normal transaminase levels and no clinical signs of liver failure. Seizures can cause elevated lactate concentrations due to anaerobic muscle activity, and the lactate typically is rapidly cleared. With no focal neurologic signs, seizures are unlikely in this patient.

The true clinical utility of serum lactate lies not in its specificity for a particular pathology but as a clinical marker of increased morbidity and mortality. An elevated lactate level should prompt an evaluation for not only causes of hypoperfusion but also for malignancy, seizure, metabolic derangements, and drug toxicity. Decreased lactate clearance has also been associated with higher mortality, particularly in patients with sepsis and after cardiac arrest.

Additional laboratory evaluation for hemolytic anemia and tumor lysis syndrome yielded negative results. On hospital day 7, the serum lactate level continued to increase to 14.7 mmol/L, WBC count increased to 28.1 × 10^9/L, LDH value was more than 2375 U/L, consistent with the diagnosis of PTLD. The patient was managed in the ICU for a total of 4 days, during which he experienced progressive renal failure, worsening encephalopathy, and finally, hepatic insufficiency. The option of hemodialysis was offered to the family but was declined. The family was updated on his prognosis, and a decision was reached to transition the patient to an inpatient hospice facility. He was transferred to hospice care that afternoon, where he later died.

5. Which one of the following end-of-life benefits is most often available exclusively through hospice vs the ICU?
   a. Adequate analgesia with opioids
   b. Pastoral care
   c. Palliative care
   d. Structured bereavement program
   e. Family support groups

Pain control at the end of life is a foremost concern. Both ICUs and hospice facilities have expertise in titrating pain medications. Additionally, both ICUs and hospices provide pastoral care through chaplains and palliative care, often guided by palliative care physicians. A structured bereavement program is available exclusively as a hospice benefit, with support and counseling to family members for 13 months after the death of the patient. Structured bereavement programs are typically not available to families of patients who die in the inpatient hospital setting. Fortunately, support groups for families often exist in both the ICU and hospice setting.

DISCUSSION

Posttransplant lymphoproliferative disorder refers to the spectrum of abnormal lymphoid proliferations, typically of B cells, occurring in the setting of ineffective T-cell function due to immunosuppression after organ transplant. Nearly all PTLDs are associated with EBV infection, and clinical severity can range from a mononucleosis-type illness to fatal rapidly proliferating non-Hodgkin lymphoma. Posttransplant lymphoproliferative disorder differs from other de novo lymphomas in that it is donor-derived from the unregulated proliferation of EBV-infected B cells in the presence of suppressed T-cell immunity after transplant.

In immunocompromised patients, EBV infects and immortalizes B cells, and without regulation by active T cells, an unchecked proliferation of EBV-positive B cells occurs, resulting in malignancy. The median onset of disease is approximately 6 months in solid organ transplants and 70 to 90 days in hematopoietic stem cell transplants. In stem cell transplants, PTLD can occur as early as 1 week after transplant, with early mortality rates nearing 90%. The mainstay of therapy in PTLD is reduction of immunosuppression, followed by rituximab and chemotherapy such as CHOP (cyclophosphamide, doxorubicin, oncovin, and prednisone), surgery, or radiation for selected cases. Rituximab is an anti-CD20 monoclonal antibody that serves as an immunotherapy-directed treatment for PTLD and is of particular use for monomorphic B-cell PTLD, substantially reducing EBV viral load. The use of rituximab has led to...
improved outcomes in PTLD, with patients receiving frontline rituximab-based therapy achieving a 3-year progression-free survival of 70%, compared with 21% for those not receiving rituximab.  

Lactate levels are often used as a measure of illness severity, a surrogate marker of mortality risk, and a tool to measure response to resuscitation efforts (such as lactate clearance in sepsis). They are most familiar to clinicians in the context of severe systemic illness. Although it is true that any form of shock or tissue hypoperfusion can cause an elevated lactate level, an elevated lactate concentration does not necessarily indicate a direct tissue/perfusion mismatch. In fact, the etiology of elevated lactate levels is diverse and in many patients, multifactorial. Lactate value should therefore not be associated as a direct marker of perfusion mismatch but rather as a poor clinical prognostic sign.  

Sepsis and septic shock lead to an elevated serum lactate level by microcirculatory dysfunction in the context of decreased oxygen extraction by peripheral tissues. Other shock states, including cardiogenic, hemorrhagic, and obstructive shock, can also lead to high lactate levels. Trauma, seizure, cardiac arrest, regional ischemia, and diabetic ketoacidosis can all lead to elevated lactate concentrations. This case illustrates a unique biochemical cause of elevated lactate level, secondary to our patient’s underlying PTLD. Tumors with high rates of proliferation, most often leukemia or lymphoma, can directly cause lactate elevation.  

Malignancy directly raises lactate levels through a diversion in cellular metabolism. In normal differentiated cells, aerobic metabolism of glucose primarily follows the pathway of the Krebs cycle and oxidative phosphorylation, leading to the highest net yield of adenosine triphosphate per unit of glucose. In tumor metabolism, glucose is utilized to fuel unregulated cellular proliferation, with the majority of pyruvate, produced from the glycolysis of glucose, metabolized to lactate, even under aerobic conditions. The remaining minority of pyruvate is processed in the mitochondria for oxidative phosphorylation. This diversion favoring lactate production in cancer cell metabolism is collectively referred to as aerobic glycolysis, better known as the Warburg effect. Patients with rapidly proliferating malignancies (such as PTLD) can thus have a markedly elevated serum lactate concentration secondary to the Warburg effect alone. The Warburg effect can lead to profound incremental elevations of serum lactate, without underlying hypoperfusion pathology.

The elevation of serum lactate levels can be categorized into 2 general categories: hypoperfusion and nonhypoperfusion. In malignancy, like in many other conditions, the level of lactate elevation is associated with a poorer prognosis. Failure to clear lactate levels after disease-directed interventions may also be a harbinger of high mortality risk. Interpretation of lactate levels must take place in the appropriate context.

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REFERENCES


CORRECT ANSWERS: 1. a. 2. c. 3. e. 4. a. 5. d.