A Case Series of Clinically Undiagnosed Hematopoietic Neoplasms Discovered at Autopsy

Varsha Podduturi, MD, Joseph M. Guileyardo, MD, Luis R. Soto, MD, and John R. Krause, MD

From the Department of Pathology, Baylor University Medical Center, Dallas, TX.

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ABSTRACT

Objectives: In the United States, autopsy rates have diminished to less than 5% during the last half of the 20th century and the beginning of the 21st century for a multitude of reasons. Many believe this results in unrecognized malignancies that could have explained a patient’s death.

Methods: We describe six deaths in which hematopoietic neoplasms were identified at autopsy but were not diagnosed clinically.

Results: The six undiagnosed hematopoietic malignancy cases discovered at autopsy include four men and two women ranging from 50 to 78 years of age. One patient was African American and five patients were white, all with multiple comorbidities. The tumors included diffuse large B-cell lymphoma, activated B-cell type, intravascular large B-cell lymphoma, ALK-negative anaplastic large cell lymphoma arising in a setting of human immunodeficiency virus, and a myeloid sarcoma.

Conclusions: These cases illustrate the importance of the traditional postmortem examination in not only confirming clinical diagnoses but also identifying previously unknown diagnoses. Hematologic malignancies may present with nonspecific clinical manifestations, and this series of cases also emphasizes the necessity for widening the differential diagnosis in patients with unexplained lactic acidosis and hepatic failure to include hematopoietic malignancies since prompt treatment may be lifesaving.

Since the 1970s, the average nonmedicolegal autopsy rate has declined to less than 5% in the United States.1 The prevalence and trust in radiographic imaging have been acknowledged as one cause of this decline. Virtual autopsy or the “virtopsy” has been opined to replace the traditional autopsy, which remains the gold standard for cause of death determination. Virtual autopsy has advantages in identifying trajectory of bullets and air emboli; however, the traditional autopsy is more advantageous for malignant and cardiovascular diseases.2 Typical clinical manifestations of hematopoietic neoplasms include lymphadenopathy and/or other “B symptoms” such as fever, weight loss, or night sweats. However, hematologic malignancies may present with subtle clinical manifestations such as lactic acidosis (LA) and hepatic failure. We present the clinical, pathology, and autopsy findings of six cases of clinically undiagnosed hematopoietic malignancies discovered at autopsy.

Materials and Methods

The following six cases are from autopsy files of Baylor University Medical Center (BUMC) at Dallas, Texas, from January 2011 to April 2014. Each case had an autopsy report, H&E slides, immunohistochemical stains, and post-mortem bacterial, mycobacterial, fungal, and viral cultures. Clinical history and data were extracted from electronic medical records. During this period, there were 285 hospital autopsies, and the autopsy rate was 3.93%. The six undiagnosed hematopoietic malignancy cases include four men and two women ranging from 50 to 78 years of age. One patient was African American and five patients were white, all with...
multiple comorbidities. Table 1 summarizes the pertinent findings from each case, and detailed discussions will not be presented.

Case 1

A 78-year-old white man with a complicated medical history underwent an elective left carotid endarterectomy at an outside hospital 1 month previously. He had left upper quadrant abdominal pain and left lower chest pain, increasing transaminitis, acute renal insufficiency, and possible *Klebsiella pneumoniae* and urinary tract infection. His admission laboratory values were significant for serum urea nitrogen, 65 mg/dL (reference range, 7-18 mg/dL); creatinine, 3.7 mg/dL (reference range, 0.6-1.3 mg/dL); aspartate aminotransferase (AST), 782 U/L (reference range, 15-37 U/L); alanine aminotransferase (ALT), 424 U/L (reference range, 12-78 U/L); alkaline phosphatase, 679 U/L (reference range, 50-136 mg/dL); and lactic acid, 5.2 mmol/L (reference range, 0.9-1.7 mmol/L). Abdominal ultrasound noted hepatosplenomegaly. He developed jaundice, and endoscopic retrograde cholangiopancreatography found bilateral hepatic duct irregularities and a diverticulum of the duodenum. After the procedure, he was noted to have encephalopathy, shock, and possible sepsis. At this time, laboratory values found a lactate dehydrogenase level of 17,117 U/L and elevated transaminases and lactic acid with a normal anion gap. He continued to decline despite aggressive therapy. Hours later, the anion gap was 25, lactic acid was 19.9 mmol/L, AST was 18,903 U/L, ALT was 5079 U/L, and alkaline phosphatase was 701 U/L. He ultimately died, and a limited abdomen autopsy was requested.

Autopsy revealed 1,150 mL of liquid and clotted blood predominantly within the left upper abdomen. The spleen weighed 1,150 g and had an area of linear capsular disruption adjacent to a 1.5-cm intraparenchymal hematoma. The liver weighed 3,660 g, and cut sections revealed a soft, yellow parenchyma with diffuse mottling and irregular congestion. There were multiple tan-white enlarged lymph nodes within the hepatoduodenal ligament. Microscopically, the spleen and lymph nodes were effaced by large atypical lymphoma cells. The liver contained massive lymphomatous involvement of the hepatic lobules and portal tracts (Image 1). The bone marrow was not involved. The atypical lymphoid cells were immunohistochemically reactive for CD20, CD79a, and MUM-1 and negative for CD10 and BCL-6, classifying the lesion as a diffuse large B-cell lymphoma, activated B-cell type. The Ki-67 proliferation rate was high at 85% to 90%.

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex/Race</th>
<th>Initial pH/Anion Gap</th>
<th>Initial Lactate Level/Final Lactate Level, mmol/L</th>
<th>Initial AST/ALT/ALK Phosphatase, U/L</th>
<th>Final AST/ALT/ALK Phosphatase, U/L</th>
<th>Spleen Weight, g</th>
<th>Autopsy Liver Weight, g</th>
<th>Diagnosis</th>
<th>Other Significant Autopsy Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78/M/white</td>
<td>7.45/11</td>
<td>7.22/25</td>
<td>5.2/19.9</td>
<td>782/424/679</td>
<td>18,903/5079</td>
<td>3,360</td>
<td>Diffuse large B-cell lymphoma, activated B-cell type</td>
<td>Diverticula of the small intestine and distal colon</td>
</tr>
<tr>
<td>2</td>
<td>67/M/African American</td>
<td>7.36/17</td>
<td>7.26/17</td>
<td>2.0/10.1</td>
<td>48/43/146</td>
<td>1,794/640</td>
<td>250</td>
<td>Diffuse large B-cell lymphoma, activated B-cell type</td>
<td>Horseshoe kidney; hypertensive cardiovascular disease</td>
</tr>
<tr>
<td>3</td>
<td>69/F/white</td>
<td>7.47/16</td>
<td>7.32/24</td>
<td>3.8/4.7</td>
<td>149/50/74</td>
<td>298/48/77</td>
<td>250</td>
<td>Intravascular large B-cell lymphoma</td>
<td>None</td>
</tr>
<tr>
<td>4</td>
<td>78/F/white</td>
<td>NA/9</td>
<td>7.24/32</td>
<td>1.4/13.9</td>
<td>30/20/73</td>
<td>233/589/323</td>
<td>250</td>
<td>Diffuse large B-cell lymphoma, activated B-cell type</td>
<td>Mucosal benign epitheloid nerve sheath tumor in the ileum</td>
</tr>
<tr>
<td>5</td>
<td>50/M/white</td>
<td>7.43/10</td>
<td>7.24/17</td>
<td>4.3/7.8</td>
<td>113/31/190</td>
<td>1468/943/588</td>
<td>2,000</td>
<td>ALK-negative anaplastic large cell lymphoma</td>
<td>Pneumocystis pneumonia; cytomegalovirus adenalinis; carcinoid tumor of appendix; cholelithiasis; nephrolithiasis</td>
</tr>
<tr>
<td>6</td>
<td>71/M/white</td>
<td>7.46/12</td>
<td>NA/9</td>
<td>2.9/NA</td>
<td>1,263/1,241/303</td>
<td>164/243/406</td>
<td>80</td>
<td>Myeloid sarcoma</td>
<td>Mild arteriol nephrosclerosis</td>
</tr>
</tbody>
</table>

ALK, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NA, not available in medical records.
Case 2

A 67-year-old African American man with a history of a T-cell lymphoma diagnosed 10 years prior within the iliac lymph nodes, a retroperitoneal mass (following autologous bone marrow transplant), prostate cancer (following irradiation), and recently diagnosed hepatic cirrhosis and ascites came to the emergency department with bloody stools, altered mental status, and generalized weakness. Admission laboratory values included serum urea nitrogen, 144 mg/dL; creatinine, 6.6 mg/dL; alkaline phosphatase, 146 U/L; AST, 48 U/L; ALT, 43 U/L; and anion gap, 17. Lactate measured 2.0 mmol/L. Computed tomography (CT) found a shrunken liver with a slightly nodular surface contour, compatible with cirrhosis; no focal hepatic mass was noted. Esophagogastroduodenoscopy to detect the source of the gastrointestinal bleed was unable to be performed due to the patient’s unstable state. Echocardiogram found a large pericardial effusion, and subsequent pericardiocentesis removed 1,100 mL of bloody fluid. Flow cytometry of the pericardial effusion revealed a monoclonal B-cell population. He became increasingly hemodynamically unstable and developed disseminated intravascular coagulopathy requiring multiple transfusions and vasopressors. Lactate dehydrogenase was 258 U/L. Lactic acid increased to 10.1 mmol/L and pH was 7.26 with an anion gap of 17. The ALT was 640 U/L; AST was 1,794 U/L, and total bilirubin was 4.0 g/dL. He eventually died under comfort care measures.

Autopsy found two areas of mucosal irregularity (1.5-2.0 cm) between the body and the antrum of the stomach. The pleural cavities contained 700 mL and 750 mL of clear serous fluid in the right and left cavities, respectively. The liver, which was diffusely cirrhotic and indurated, weighed 1,150 g. The pericardium and epicardium of the heart were covered by a fibrinous exudate. Microscopically, the gastric biopsy specimen and sections from the mucosal irregularities showed fragments of gastric mucosa with a dense lymphoid infiltrate composed of large atypical cells. There was brisk mitotic activity with some apoptotic debris. The lymphoid cells were immunohistochemically positive for CD20, CD79a, MUM1, and CD22 and negative for CD10 and BCL6, consistent with a diffuse large B-cell lymphoma, activated B-cell type. Tumor cells were also identified in the spleen and the pericardium. The bone marrow was negative. There was no evidence of residual T-cell lymphoma or prostatic adenocarcinoma.

Case 3

A 69-year-old white woman with a medical history of hypertension and fatigue and nonspecific symptoms of several months’ duration recently developed fever and was given antibiotics by her primary care physician. Two weeks later, she collapsed at home and was transported to an outside hospital where she was hospitalized for several days. Despite extensive workup, a definitive diagnosis was not established. She was discharged but came to the BUMC emergency department 1 day later. Admission laboratory values were significant for WBC count, 8.2 K/mL; hemoglobin, 11.4 g/dL (reference range, 12.0-16.0 g/dL); hematocrit, 34.5% (reference range, 36.0%-47.0%); and platelet count, 128 K/mL (reference range, 140-440 K/mL). Other laboratory values included alkaline phosphatase, 74 U/L; AST, 149 U/L; ALT, 50 U/L; lactate dehydrogenase, 2,070 U/L (reference range, 100-190 U/L); lactic acid, 3.8 mmol/L (pH 7.47); and anion gap, 16. Chest x-ray revealed a 4.3 × 2.4-cm mediastinal mass and bilateral pleural effusions but no focal hepatic mass. She developed hypotension, and sepsis was clinically suspected. The next day, lactic acid increased to 4.7 mmol/L, pH was 7.32, and anion gap was 24. Other significant laboratory values were lactate dehydrogenase, 2,070 U/L; AST, 298 U/L; ALT, 48 U/L; and alkaline phosphatase, 77 U/L. Two days after admission, she died under comfort care measures.

Autopsy found a normally developed, moderately obese woman with bilateral pleural effusions (right, 730 mL; left, 690 mL). The spleen weighed 250 g with surrounding lymphadenopathy. The liver weighed 1,400 g, and the cut surface revealed multiple tan, circumscribed nodules (0.2-1.8 cm). There was a thrombus in the left brachiocephalic vein associated with central catheter placement through the left jugular vein. Microscopically, there were atypical lymphoid cells within the lumina of small
vessels in most organs and tissues throughout the body, most prominent in the lungs. The lymphoid cells were enlarged with pleomorphic, vesicular nuclei and prominent nucleoli, and numerous mitotic figures were identified. Histologically, the lymph nodes exhibited an effacement of normal nodal architecture by the same atypical lymphoid cells. Immunohistochemically, these lymphoid cells expressed CD20 and MUM-1 and were negative for CD3, CD30, CD15, CD10, and BCL-6. Ki-67 was 50%. Tumor was both intravascular and extravascular and identified in the left adrenal gland, liver, right atrial wall, appendix, bladder, and liver, as well as in numerous blood vessels, including the brachiocephalic vein, pelvic veins, and connective tissue surrounding the thyroid gland. This tumor was classified as an intravascular large B-cell lymphoma with extravascular involvement of various organs. Scattered atypical lymphoid cells were present within the bone marrow. The mediastinal mass previously described by radiographic imaging was a hematoma contiguous with the airway or contribute to death.

Case 4

A 78-year-old white woman with no significant medical history who recently developed memory difficulties fell and hit her head. Admission laboratory values showed the following: WBC count, 4.7 K/µL; hemoglobin, 10.6 g/dL; hematocrit, 32.3%; platelets, 187 K/µL; alkaline phosphatase, 73 U/L; AST, 30 U/L; and ALT, 20 U/L. Lactic acid measured 1.4 mmol/L. CA-125 and CEA were within normal limits. Anion gap measured 9. Radiographic imaging found a 2.7-cm mass in the left basal ganglia with surrounding multiple smaller masses within the brain parenchyma. The liver was unremarkable. An attempted biopsy of the brain mass was unsuccessful. Liver function tests increased over the next few days, with an alkaline phosphatase of 339 U/L, AST of 454 U/L, and ALT of 396 U/L. Postoperatively, the patient’s condition continued to decline, including a persistent anion gap metabolic acidosis and an elevated lactic acid of 13.9 mmol/L. Liver function tests remained abnormal, and 11 days after admission, the patient died. A limited head, abdomen, and pelvis autopsy was requested.

At autopsy, the liver weighed 1,725 g, and the parenchyma was finely speckled. There was a 1.5 × 2.5-cm ill-defined mass with a 0.6 × 0.4-cm area of hemorrhage in the left cerebral caudate lobe. The spleen weighed 250 g, and the cut surface was diffusely. Histology revealed extensive infiltrates of large atypical lymphocytes with convoluted nuclei and prominent nucleoli in the spleen and in the portal tracts of the liver. Similar atypical cells were identified in the adrenal gland and in several lymph nodes. These atypical cells stained positively for CD20, MUM1, CD22, and CD79a and were negative for Alk-1, CD10, and CD30. This is consistent with a diffuse large B-cell lymphoma, activated B-cell type. Many perivascular lymphomatous infiltrates were found in the skeletal muscle, kidney, uterus, and pituitary gland. Bone marrow was 50% to 60% cellular with a few collections of markedly atypical lymphoid cells consistent with lymphomatous involvement.

Case 5

A 50-year-old white man with a medical history of recently diagnosed human immunodeficiency virus (HIV) had a 1-month history of decreased energy, malaise, night sweats, and a 20-pound weight loss. Initial laboratory values were significant for anemia and thrombocytopenia. Laboratory values were as follows: lactate, 4.3 mmol/L; AST, 113 U/L; ALT, 31 U/L; alkaline phosphatase, 190 U/L; pH 7.43; and anion gap, 10. Chest x-ray found bilateral pulmonary infiltrates, and he was started on trimethoprim/sulfamethoxazole for presumed pneumocystis pneumonia. Abdominal ultrasound found 1.6-cm and 1.3-cm masses in the left and right hepatic lobes, respectively, and multiple enlarged lymph nodes. His respiratory function declined, requiring intubation and mechanical ventilation. His creatinine increased, and dialysis was initiated. He had a persistent elevated lactate level (7.8 mmol) and anion gap of 19. His liver function progressively declined, and anion gap measured 17 and pH was 7.24. Despite supportive and therapeutic measures, his condition deteriorated, and he died.
Autopsy found bilateral pleural effusions (right, 400 mL; left, 400 mL) and a pericardial effusion (120 mL). The liver weighed 2,000 g, and cut sections found two tan-white, fleshy, well-circumscribed intraparenchymal nodules. The remainder of the parenchyma was tan-red. The spleen weighed 1,050 g, and cut sections found normal red pulp with indistinct white pulp and numerous subcapsular solid tan-white, flat lesions. There was massive and diffuse lymphadenopathy with lymph nodes up to 4.0 cm within the abdomen. The lymph nodes were infiltrated by large, atypical lymphocytes with prominent nucleoli. Multinucleated cells were also identified. The atypical lymphocytes stained positively for CD30 and focally positive for EMA and CD3. The atypical lymphocytes were immunohistochemically negative for ALK-1, PAX5, CD43, CD56, HHV-8, TIA-1, CD5, CD7, CD4, BCL6, CD10, and CD20. Epstein-Barr virus–encoded small RNA by in situ hybridization was strongly positive. T-cell receptor γ gene rearrangement and IgH receptor gene rearrangement were attempted and unable to yield diagnostic results due to the poor quality of DNA present in the sample. Ki-67 measured 20% to 25%, with focal 60% to 65% positivity. In summary, this was diagnosed as an ALK-negative anaplastic large cell lymphoma arising in a setting of HIV. Tumor was also present in the liver, kidney, and spleen.

Case 6

A 71-year-old white man with a medical history of acute myelogenous leukemia (FAB M2) requiring allogeneic bone marrow transplant 1 year ago with a relapse 6 months later had right heart failure and elevated liver transaminases and creatinine levels. Other laboratory values were as follows: WBC count, 13.0 K/μL; hemoglobin, 14.6 g/dL; hematocrit, 43.2%; platelets, 42 K/μL; and lactic acid, 2.0 mmol/L. His peripheral blood and bone marrow studies showed remission of leukemia. However, he developed bradycardia requiring pacemaker placement and progressive right heart failure. Antemortem echocardiography and chest CT led to a clinical impression of atrial septal defect and pericardial effusion. Repair of the atrial septal defect was considered, but he became increasingly hypotensive. Nine days after admission, he died, and an autopsy was requested.

At autopsy, there was a pericardial effusion (75 mL). The heart weighed 740 g, and the right atrium was almost entirely filled with tumor. The left atrial wall and atrial septum were also diffusely infiltrated by tan-white tumor. There were multiple nodules present within the gastric mucosa (0.5-9.0 cm). Histologically, the tumor was composed of solid sheets of atypical immature cells and frequent mitotic figures. The tumor cells stained positive for CD34 and CD68 by immunohistochemical stains and were diagnosed as a myeloid sarcoma. Leukemic cells were also identified in the stomach, bowel, lung, and kidney. Other significant autopsy findings included mild arteriolar nephrosclerosis.

Discussion

These cases highlight the value of a traditional autopsy in establishing a correct diagnosis. Over the past 50 years in the United States, the autopsy rate has fallen from a high of 41% in the 1960s to less than 5% currently. The reasons for the decline of clinical autopsy rates are varied, complex, and numerous, including lack of reimbursement, family unwillingness to consent for autopsy, and trust in modern diagnostic clinical techniques. Some autopsies are not pursued for fear of potential litigation, but in most instances, the postmortem examination exonerates the hospital staff. Other benefits of the traditional autopsy include medical education through clinicopathologic correlations and conferences.

The virtual autopsy, also known by the portmanteau virtopsy, has been lauded as a noninvasive, image-based alternative to traditional autopsy examination. Virtual autopsy involves postmortem magnetic resonance imaging or CT in combination with software to create 3-dimensional images. These radiographic techniques have been helpful in identifying bullet paths, bone fractures, and air or gas emboli. However, the detection of pulmonary emboli, cardiovascular disease, and malignant tumors by imaging has its limitations. In a prospective study performed by Wichmann et al comparing diagnoses between virtual autopsy and
traditional autopsy, cardiovascular disease and malignancies were more often missed with a virtual autopsy than with a conventional autopsy. Therefore, traditional internal and external postmortem examination remains the gold standard, especially in hematologic and oncologic malignancies.\(^4\) Identifying lymphomatous involvement of solid organs by radiographic imaging is especially problematic, as illustrated by cases 1, 5, and 6 presented in this article.

As noted previously, hematopoietic neoplasms may solely have nonspecific clinical manifestations such as LA and/or hepatic failure. LA is subdivided into two distinct categories.\(^7\) Type A is associated with tissue hypoperfusion or hypoxemia. Type B occurs when lactate accumulates despite adequate oxygen levels and tissue perfusion. Luft et al\(^8\) defined type B LA as pH 7.35 or less and serum lactate levels of 5.0 mmol/L or more as a severe metabolic complication associated with leukemia or lymphoma. However, a multitude of other conditions are associated with type B LA, including medical disease (liver failure, renal failure, HIV), medications (metformin, salicylates, isoniazid, cyanide), toxins, and hereditary disorders (pyruvate dehydrogenase deficiency).\(^8\) Lymphoma is uncommonly associated with type B LA, but this finding forecasts a poor prognosis.\(^7\)

The precise pathophysiology of LA in hematologic malignancies is unknown, but several mechanisms have been postulated. Two potential causes include decreased metabolism of lactate by the kidney and liver dysfunction. Lactate is the end product of anaerobic glycolysis and is converted to glucose and then pyruvate by both the liver and kidney. A majority of the lactate is cleared by the liver and, to a lesser extent, by the kidneys.\(^7\) The kidneys and liver may be compromised by direct infiltration of tumor, ischemia, or other injurious factors.\(^7\)

Many of the patients presented here had both kidney and liver dysfunction, but it is difficult to determine the relative contribution of each. Also of note is that many patients with liver and/or renal dysfunction do not develop LA.\(^7\)

Another hypothesis of LA in hematologic malignancies involves mitochondrial dysfunction and overexpression of glycolytic enzymes such as insulin-like growth factor 1 and hexokinase by tumor cells, which leads to high rates of glycolysis and therefore higher glucose levels, which allow the cells to multiply at a rapid rate.\(^10,11\) Neoplastic cells often use anaerobic metabolism even in the presence of oxygen, which results in a large percentage of glucose converted to lactate.\(^7\) Anaerobic glycolysis may also occur when tissue perfusion is diminished by a heavy tumor burden or tumor microemboli.\(^12\)

Tumor lysis syndrome has also been postulated as a cause in the development of type B LA.\(^13\) Apoptosis of tumor cells causes a loss in the mitochondrial membrane potential and in a loss of mitochondrial function.\(^13\) This results in compensatory glycolysis in these cells, which causes lactate accumulation and acidosis.\(^13\)

In the 1920s, Otto Warburg discovered that tumor cells metabolize more lactate than nonneoplastic cells. When comparing lactate production and oxygen consumption of nonneoplastic liver tissue vs liver carcinoma from rats, Warburg and colleagues discovered that normal tissue showed inhibition of lactate production in the presence of oxygen (termed the Pasteur effect).\(^14,15\) However, cancer cells tend to “ferment” glucose into lactate even in the presence of adequate oxygen.\(^14,15\) The advantage that this type of metabolism confers to cancer cells is currently unclear and is under intense investigation.
In many cases, identifying the source of LA is clinically challenging. Also, patients with type B LA who progress to type A LA have a lower survival due to high levels of lactate and a concomitant acidosis, with increased risk of being refractory to aggressive medical intervention. Clinicians should recognize type B LA as early as possible and remain cognizant of potentially reversible etiologies. An increased index of suspicion for hematologic malignancies may lead to lifesaving treatment, but outcome depends on the responsiveness of the underlying tumor to treatment.\(^\text{10}\)

Acute liver failure as the initial presentation of hematopoietic malignancies is uncommon. In rare cases, lymphomatous infiltrates in the hepatic parenchyma result in ischemia due to sinusoidal infiltration or replacement of the liver parenchyma with malignant lymphoid cells,\(^\text{16,17}\) and clinical features of lymphoma associated with acute hepatic failure include hyperbilirubinemia, elevated transaminases (AST > ALT), and elevated serum lactate levels\(^\text{18}\) as noted above. This presentation is uncommon and not usually considered in patients with hepatic failure, which may potentially result in a delayed diagnosis.\(^\text{18}\)

**Conclusion**

This series of cases further confirms that traditional autopsy remains a reliable tool in elucidating accurate diagnoses. Postmortem imaging should be regarded as a complement to traditional autopsy, but it is not a replacement, and even if a tumor is found by imaging, histologic classification still depends on microscopic and molecular studies. The presence of type B LA remains a possible clue to underlying hematopoietic neoplasms and should be documented early when feasible.

 Address reprint requests to Dr Podduturi: Dept of Pathology, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246; varsha.podduturi@gmail.com.

**References**