CASE REPORT

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Polyclonal Systemic Immunoblast Proliferation: An Unusual Hematologic Entity Presenting as a Medical Examiner Case*

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ABSTRACT: A 43-year-old woman who was receiving oral antibiotics for several days for a superficial foot infection developed a persistent rash, fever, and lymphadenopathy, despite discontinuation of the antibiotic and administration of steroids for a presumed drug reaction. Hours after a subsequent visit to the emergency room for worsening symptoms, she died at home. At autopsy, there was a florid, systemic proliferation of polyclonal plasma cells and immunoblasts infiltrating nearly every organ and tissue of the body, most notably the lymph nodes and spleen. The polyclonal nature of the process was confirmed by immunofixation electrophoresis and immunohistochemistry. Cases of fatal polyclonal systemic immunoblast proliferations are extremely rare, and the trigger for such proliferations is not always known. We review the literature on this unusual entity and discuss the clinical and pathologic findings.

KEYWORDS: forensic science, forensic pathology, polyclonal, immunoblasts, sepsis, fatal

A florid, systemic immunoblastic and plasma cell infiltrate is a rare condition of uncertain etiology. Though polyclonal in nature, the entity can be as deadly as a hematopoietic cancer. This entity has been described in a small series of patients (1), and more recently as a case report (2). In this report, we describe the case of a patient being treated for what was clinically thought to be a drug reaction. Despite some relief of her symptoms with therapy, and partial (albeit inadvertent) treatment of her underlying hematologic problem, the patient succumbed at home to sepsis complicating her undiagnosed polyclonal systemic immunoblast proliferation. To our knowledge, this is the first report of undiagnosed systemic polyclonal immunoblast proliferation resulting in unexpected, out of hospital death and presenting as a medical examiner's case.

Case History

The decedent was a 43-year-old white female with no significant medical history except "allergies" to several antibiotics. She had been placed on oral ciprofloxacin 12 days prior to her death for a superficial infection of her left foot. Six days later she returned to her physician with a generalized pruritic rash, slight headache, low-grade fever, and swollen lymph nodes. Ciprofloxacin therapy was discontinued and tapering doses of oral prednisone begun.

One day prior to her death she was nauseated and vomiting, taking in only liquids. She presented to the emergency room, where she had pruritic urticaria of the face, neck, trunk, and extremities. She also had tender, firm adenopathy of the neck. Intravenous diphenhydramine and cimetidine offered some relief of her continued itching. Her white blood cell count was elevated at 29.5×10^9/L (normal $4 \times 10^9 - 11 \times 10^9$/L), with a left shift. The erythrocyte sedimentation rate was 56 mm/h (normal 0–20 mm/h). A heterophil test for mononucleosis was negative. After returning home, her breathing became shallow and she asked her son for help getting off the toilet. When she stopped talking, her son thought she had fallen asleep, so he returned to bed. When discovered dead by her son five hours later, she was still seated on the toilet. Rigor was present; livor could not be assessed due to her extensive rash.

Pathologic Findings

Gross Findings

Autopsy demonstrated an obese Caucasian female free of trauma. With the exception of the face, palms, and soles, the skin was diffusely covered with a red, petechial rash (Fig. 1). Scattered areas contained slightly larger, encrusted lesions, and excoriations were on the lower abdomen and thighs. The spleen was enlarged (720 g), with firm red parenchyma admixed with large areas of pink-red necrosis. Lymph nodes throughout the body were massively enlarged, with red and white mottling of the cortices and medullae. The liver was heavy (2720 g), without focal lesions. Both kidneys were pale and boggy. Subendocardial mottling was present on the left side of the interventricular septum. The thymus was unusually prominent for age. The brain was unremarkable.

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Histologic Findings

All tissues retained at autopsy were fixed in 10% formalin and routinely processed. The lymph nodes demonstrated florid expansion of the interfollicular areas by a mixture of small lymphocytes, plasma cells, and immunoblasts (Fig. 2). Immunohistochemical staining confirmed the lymphocytes and immunoblasts to be a mixture of B (CD20+ and MB2+) and T (CD3+ and CD45RO+) cells, while the plasma cells were a mixture of kappa- and lamba-positive cells. The antemortem peripheral smear, obtained the evening before the patient died, showed neutrophil vacuolization and toxic granulation. Circulating plasma cells and immunoblasts were also present (Fig. 3). The red and white pulp of the spleen was expanded by a population of cells identical to that in the lymph nodes. The heart (Fig. 4*A*), liver (Fig. 4*B*), kidneys (Fig. 4*C*), thymus, pancreas, thyroid, adrenal glands, lungs, and skin all contained similar infiltrates. The lymph nodes and the spleen contained large areas of necrosis. The bone marrow showed 80 to 90% cellularity, with expansion of the granulocyte compartment. Plasma cells, a mixture of kappa- and lamba-positive, were increased in the marrow space. The brain was microscopically unremarkable.

Laboratory Findings

Blood volatile and drug screens were negative. Vitreous electrolytes were remarkable only for a urea nitrogen of 21.8 mmol/L (normal 3.6–7.1 mmol/L). Serum protein electrophoresis showed a polyclonal hypergammaglobulinemia. Immunoglobulin levels were IgG 20.4 g/L (normal 5.6–14.6 g/L), IgA 6.4 g/L (normal 0.6–3.1 g/L), and IgM 2.2 g/L (0.4–2.4 g/L). No clonal bands were identified by immunofixation electrophoresis. HIV-1/HIV-2 antibody tests were nonreactive. Postmortem blood culture grew *Clostridium paraputrificum.*

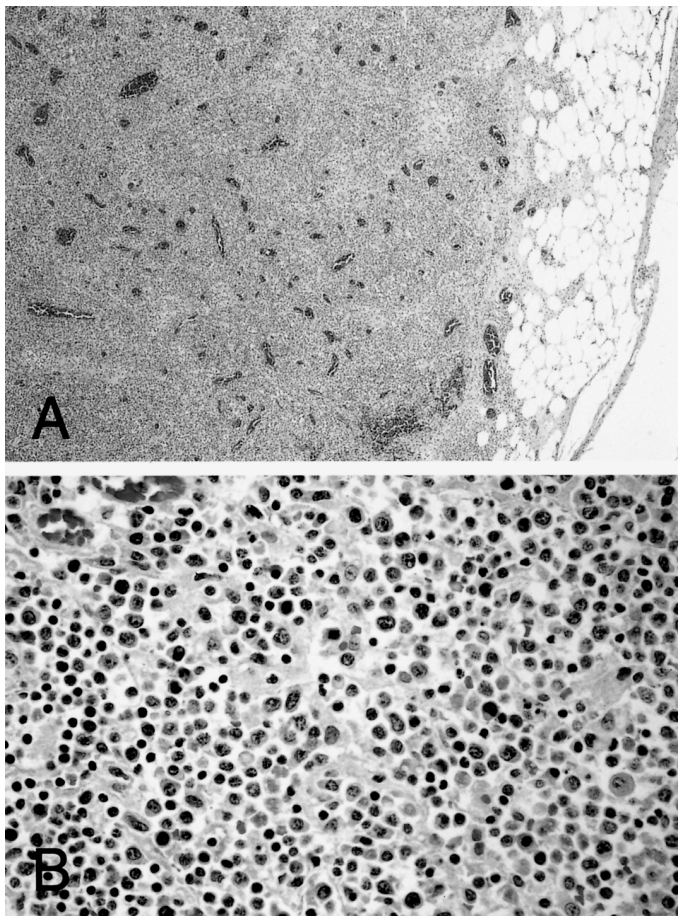

FIG. 2—(A) *Effacement of lymphoid architecture, with lymphoid cells infiltrating into pericapsular fat (hematoxylin-eosin).* (B) *Heterogeneous lymphoid population within lymph node (hematoxylin-eosin).*

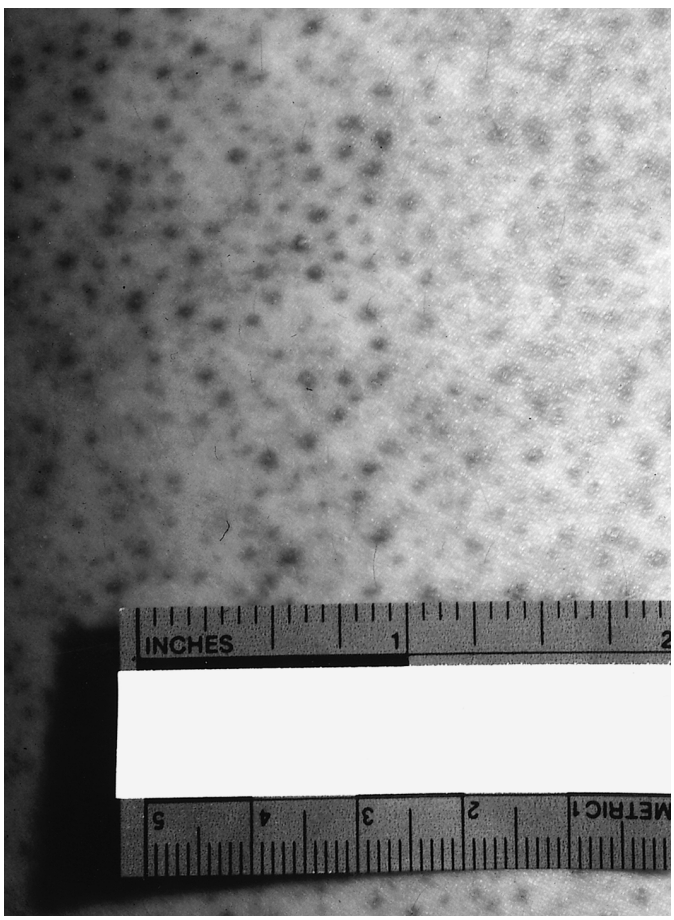

FIG. 1—*Diffuse, finely papular, petechial rash.*

Discussion

Immunoblasts are medium or large, transformed lymphoid cells with immunologic features of B or T lymphocytes. The T immunoblasts give rise to T lymphocytes, while B immunoblasts are precursors of plasma cells or memory B cells (3). Immunoblasts are actively proliferating cells that are normally found in lymphoid tissue (4). A reactive, non-neoplastic plasmacytic-immunoblastic infiltrate can occur in the lymph nodes of patients with several different disorders, including viral lymphadenitis (3), drug-related lymphadenopathy (4), non-viral infections (4), infectious mononucleosis (5), autoimmune diseases, and angioimmunoblastic lymphadenopathy.

Peterson et al. described a series of four patients (three female, one male) with polyclonal systemic immunoblast proliferation (1). All of the patients presented with fever, and all had various combinations of dyspnea, rash, generalized lymphadenopathy, and hep-

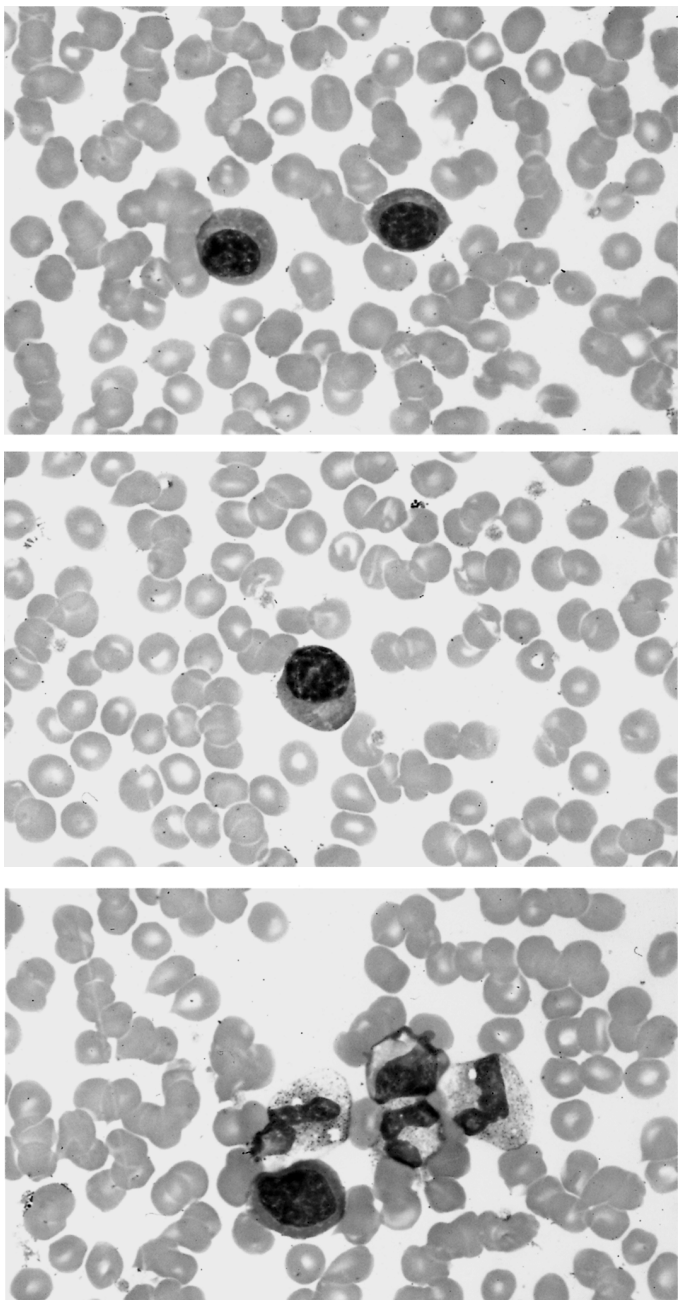

FIG. 3—*Antemortem peripheral blood smear with circulating immunocytes; also note marked toxic granulation and vacuolization of granulocytes in lowest panel (Wright stain).*

atosplenomegaly. In the peripheral blood, immunocytes (plasma cells and immunoblasts) represented 23 to 39% of the total leukocyte population; in the bone marrow sections, they represented 15 to 30% of the total marrow cell population. Lymph nodes biopsied in two of the patients showed near total effacement by lymphocytes, plasma cells, and immunoblasts. Although immunohistochemical studies of bone marrow core sections demonstrated a polyclonal infiltrate in all four cases, two of the cases did have a pseudodiploid clone, with a translocation involving 14q32, by cytogenetic analysis. Two of the patients were alive and well, without recurrence, after treatment; one patient died of complications of *Staphylococcus aureus* sepsis, one (who also had AIDS) of multisystem organ failure.

A similar case was described by Poje et al. in a 50-year-old man with fever and jaundice (2). The portal tracts of the liver were expanded by a heterogeneous population of lymphocytes and immunocytes, elevated numbers of plasma cells were in the peripheral blood and bone marrow, and serum protein electrophoresis demonstrated polyclonal hypergammaglobulinemia. Intravenous corticosteroid administration resulted in rapid clinical improvement, and the patient remained disease-free at one year.

In the absence of a clinical syndrome (i.e., viral), the antigenic stimulus for a polyclonal, systemic immunoblast proliferation is

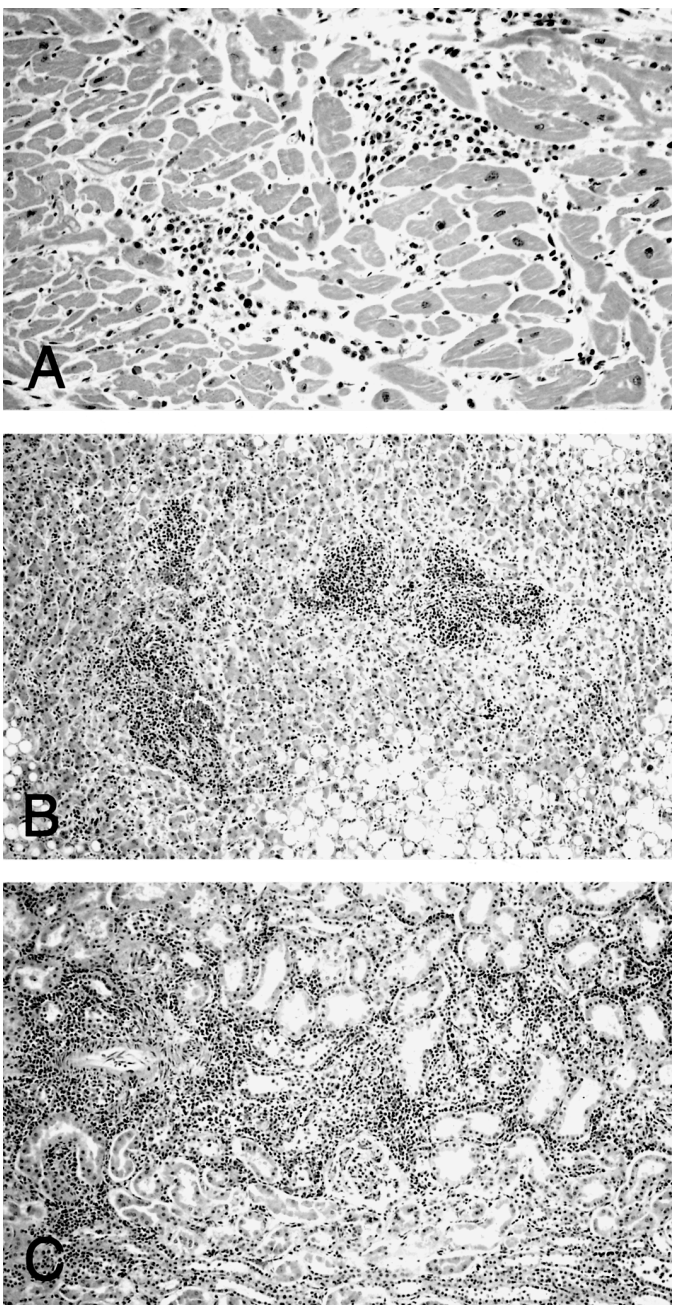

FIG. 4—(A) *Lymphoid infiltrate in myocardium (hematoxylin-eosin).* (B) *Lymphoid infiltrate expanding portal tracts in liver (hematoxylin-eosin).* (C) *Lymphoid infiltrate in kidney (hematoxylin-eosin).*

rarely identified (1,4). Drugs, other infectious agents, and chemicals have been suggested as triggers, either alone or in concert (1). In many cases, the process will be more localized and self-limited.

The extent of necrosis, within the lymph nodes and spleen, in this case likely reflects the administration of prednisone, which was given for a presumed drug reaction. Corticosteroid therapy would be expected to have a negative effect on a rapidly proliferating lymphoid population. Indeed, corticosteroid therapy has been a component of successful treatment in some previously described and diagnosed cases of polyclonal systemic immunoblast proliferation (1,2).

In retrospect, the patient's antemortem peripheral smear was highly suggestive of impending or ongoing sepsis, manifesting a left-shifted differential with striking granulocyte vacuolization and toxic granulation. We believe the autopsy blood culture of *Clostridium paraputrificum* confirmed sepsis as the terminal mechanism of this patient's hematologic abnormality. *Clostridium paraputrificum*, which is found in the normal human gastrointestinal tract, is a rare cause of disease in humans but has caused well-documented cases of sepsis in certain clinical situations, including immunodeficiency (6,7).

The distinction between benign, premalignant, and malignant lymphoid processes is difficult. Increased numbers of plasma cells and immunoblasts in the blood, bone marrow, and lymph nodes, with immunohistochemical and laboratory data indicating a polyclonal process, should allow the correct diagnosis to be made (2). Polyclonal systemic immunoblast proliferation is a rare entity that should be included in the differential diagnosis of lymphoid proliferations. As this case points out, this is true not only for the hospital-based pathologist, but for the forensic pathologist as well.

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