Intravascular Large B Cell Lymphoma: An Elusive Cause of Pyrexia of Unknown Origin Diagnosed Postmortem

N. E. Holmes, C. L. Gordon, N. Lightfoot, P. Crowley, R. R. Buchanan, C. L. Smith, and P. D. R. Johnson

Departments of Infectious Diseases, Anatomical Pathology, Rheumatology, and Haematology, Austin Health, Heidelberg, and Department of Medicine, University of Melbourne, Melbourne, Australia

Intravascular large B cell lymphoma (IVLBCL) is a rare cause of pyrexia of unknown origin. Because of its protean clinical manifestations, diagnosis is elusive and is often made postmortem. We report here a case of IVLBCL that evaded diagnosis despite multiple investigations in vivo for pyrexia of unknown origin over a 5-month period.

A 66-year-old retired textile worker was admitted with a 2-week history of daily temperatures >38°C, night sweats, anorexia, weight loss (2 kg), intermittent productive cough, and exertional dyspnea. Her comorbidities included diabetes mellitus, hypertension, dyslipidemia, and asthma. She migrated to Australia from the Philippines in 1981 and had visited family there during the previous year. Examination revealed a systolic flow murmur and a temperature of 38.2°C. Initial investigations revealed normal complete blood count, an elevated erythrocyte sedimentation rate (ESR) of 97 mm/h, and a C-reactive peptide (CRP) level of 249.8 mg/L. Her sodium concentration was 128 mmol/L, and she had abnormal liver function (alkaline phosphatase [ALP] level, 158 IU/L; alanine aminotransferase [ALT] level, 132 IU/L; γ-glutamyltransferase [GGT] level, 79 IU/L; and lactate dehydrogenase [LDH] level, 570 IU/L). Results of computed tomography (CT) of the chest and abdomen with intravenous contrast were normal, apart from a 2–3-cm hypodensity initially seen. Liver biopsy revealed nonspecific mild inflammation, with no neoplasia or granulomas. Results of lactate dehydrogenase; and thyroid function were normal. Hemolysis was not performed. Protein electrophoresis (serum and urine); levels of immunoglobulins, T cell subsets, cold agglutinins, cryoglobulins, autoantibodies, serum angiotensin–converting enzyme; and thyroid function were normal. Hemolysis was absent. Abdominal ultrasound and magnetic resonance cholangiopancreatography failed to demonstrate the hepatic hypodensity initially seen. Liver biopsy revealed nonspecific mild inflammation, with no neoplasia or granulomas. Results of laryngoscopy, gastroscopy, whole-body contrast CT (brain, chest, abdomen [repeated], and pelvis), transthoracic echocardiography, small bowel biopsy, temporal artery biopsy, and bone marrow aspirate and trephine biopsy were normal. In particular, there was no evidence of Whipple disease, vasculitis, hemophagocytosis, abnormal bone marrow by flow cytometry, or lymphadenopathy. Whole-body positron emission tomography (PET) with 18F-fluorodeoxyglucose revealed a small focus of increased uptake in the small bowel thought to be of no significance.

During the fourth week of hospitalization, she developed a sepsis, and she was placed in respiratory isolation pending the results of sputum mycobacterial smears.

She continued to have temperatures to 40°C, and antibiotics were ceased after 1 week pending further investigation. Results of blood, urine, and sputum cultures for bacteria (including extended incubation) and mycobacteria were negative. During the next 4 weeks, she underwent multiple investigations. She had serological evidence of past infection with cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6. Human immunodeficiency virus serological results were negative, and tuberculin skin test results were 0 mm with an indeterminate Quantiferon-TB Gold (Cellestis) assay result. Nasopharyngeal swab results were negative for respiratory viruses on day 2 of hospitalization but became positive for picornavirus on day 20. Serological results for atypical and fastidious organisms (including Bartonella species, Brucella species, Borrelia species, Legionella species, Coxiella species, Toxoplasma species, Burkholderia pseudomallei, and Leptospira interrogans) and viruses (including flavivirus, human T lymphocytic virus, parvovirus, and hepatitis A, B, and C viruses) were negative. Results of peripheral blood smears were negative for malarial and other parasites. An orthopantogram demonstrated licency and cortical irregularity in a single maxillary molar, but she denied dental symptoms. A dental review excluded a dental source of pyrexia of unknown origin (PUO).

Serum ferritin and β2-microglobulin levels were 1079 μg/L and 5.7 mg/L, respectively. Analysis of LDH isoenzymes was not performed. Protein electrophoresis (serum and urine); levels of immunoglobulins, T cell subsets, cold agglutinins, cryoglobulins, autoantibodies, serum angiotensin–converting enzyme; and thyroid function were normal. Hemolysis was absent. Abdominal ultrasound and magnetic resonance cholangiopancreatography failed to demonstrate the hepatic hypodensity initially seen. Liver biopsy revealed nonspecific mild inflammation, with no neoplasia or granulomas. Results of laryngoscopy, gastroscopy, whole-body contrast CT (brain, chest, abdomen [repeated], and pelvis), transthoracic echocardiography, small bowel biopsy, temporal artery biopsy, and bone marrow aspirate and trephine biopsy were normal. In particular, there was no evidence of Whipple disease, vasculitis, hemophagocytosis, abnormal bone marrow by flow cytometry, or lymphadenopathy. Whole-body positron emission tomography (PET) with 18F-fluorodeoxyglucose revealed a small focus of increased uptake in the small bowel thought to be of no significance.

During the fourth week of hospitalization, she developed a
symptomatic *Escherichia coli* urinary tract infection that was treated with trimethoprim. The patient declined a trial of corticosteroids. She defervesced over the next week, with normalization of ESR level, CRP level, and liver function, and she was discharged home on hospitalization day 35. She remained afebrile over the next 2 months, with normal blood test results.

She was then readmitted with fevers and sweats with recurrent cough, exertional dyspnea, and headache. Physical examination was unremarkable. Again she had elevated ESR (97 mm/h) and CRP (342 mg/L) levels with hyponatremia (126 mmol/L) and liver abnormalities (ALP level, 147 IU/L; ALT level, 94 IU/L; GGT level, 153 IU/L; and LDH level, 948 IU/L). Bacterial cultures (including mycobacterial cultures), peripheral blood smears, abdominal ultrasound, and whole body CT with intravenous contrast (including sinuses) were repeated, and results were normal. Results of cerebrospinal fluid examination, mesenteric angiography, cerebral magnetic resonance imaging and angiography, and transoesophageal echocardiography were also normal. A second bone marrow aspirate and trephine biopsy demonstrated mild lymphocytosis and a small interstitial lymphoid aggregate, likely to be reactive in nature, with no evidence of a clonal B cell or abnormal T lymphoid population on flow cytometry. There were no granulomas or hemophagocytosis. An infectious etiology was considered less likely, and the patient commenced a trial of daily prednisolone (50 mg).

Within 4 days of corticosteroid commencement, she became dramatically unwell, with hypotension, hypoglycemia, and abdominal pain. She developed progressive thrombocytopenia (platelet concentration, $43 \times 10^9$ cells/L), acute renal impairment (creatinine level, 193 $\mu$mol/L), hepatic failure (ALP level, 295 IU/L; ALT level, 258 IU/L; and GGT level, 218 IU/L), hyperphosphatemia (2.28 mmol/L), tachypnea, and severe metabolic acidosis. Empiric meropenem, doxycycline, fluconazole, rifampicin, isoniazid, moxifloxacin, and amikacin was commenced to cover for sepsis and tuberculosis, possibly unmasked by corticosteroid treatment. She was transferred to the intensive care unit (ICU) and developed progressive multiorgan failure. Despite maximal inotropic and ventilatory support, she rapidly deteriorated and died within 12 h of ICU admission (day 22 of the second hospitalization).

Postmortem examination revealed disseminated intravascular large B cell lymphoma (IVLBCL) within multiple organs, including bone marrow (despite negative results for 2 in vivo bone marrow aspirate and trephine biopsies), lungs, thyroid, adrenals, liver, kidneys, pancreas, heart, gastrointestinal tract,

Figure 1. Strongly positive CD20 immunostaining of lymphoma cells within a blood vessel.
spleen, and peripheral blood. There were no lymphadenopathy or extranodal tumor masses. All microbiology specimens were culture negative for tuberculosis. Immunophenotyping was positive for CD10, CD20, and bcl-2 (Figure 1).

IVLBCL is the “oncologist’s great imitator” [1]. It is a rare subtype of extranodal diffuse large B cell lymphoma characterized by the involvement of lumina of small vessels [2] and aggressive disease progression. It is frequently diagnosed postmortem and manifests as a PUO. Lymphadenopathy is usually absent. In a series by Murase et al [3], the most common abnormalities were hematological. There appear to be racial clinical variations, possibly due to ethnic differences in cytokine production [4]; cutaneous and central nervous system disease is prominent in Europeans, whereas hemophagocytic syndrome, hepatosplenomegaly, and thrombocytopenia are prominent in Asians. Diagnosis is made on the basis of bone marrow or solid organ biopsy results. PET scanning is not as helpful as it is for nodal lymphoma, because of low numbers of tumor cells per volume and selective growth within the lumina of small vessels [2]. The suggested workup for IVLBCL proposed by Ponzoni et al [5] did not yield an in vivo diagnosis for this patient. Combination chemotherapy with rituximab is the treatment of choice, although local radiotherapy can be performed for limited cutaneous disease. Prognosis is poor except for cutaneous disease [3, 4].

Our patient underwent extensive noninvasive and invasive testing and multimodal imaging without yielding an in vivo diagnosis. In light of the final diagnosis, previous imaging and biopsies were re-reviewed, but the diagnosis was not evident, even in retrospect. The utility of bone marrow examination for PUO was recently evaluated by Hot et al [6], and it was found to be most useful if anemia or thrombocytopenia is present. These abnormalities did not occur until our patient’s second hospitalization, and her second bone marrow examination was nondiagnostic. Mourad et al [7] have described a comprehensive approach to the evaluation of PUO, and performing all of these investigations also failed to reveal a diagnosis. This case highlights the physician’s dilemma in investigating PUO, in particular how far to continue with noninvasive and invasive investigations. Patient well-being and avoiding iatrogenic complications, as well as economic costs, need to be considered and balanced.

In a prospective case series of patients with PUO by Bleeker-Rovers et al [8], remission of PUO occurred with no ultimate diagnosis in 51% of cases. Interestingly, our patient had complete remission of fever and laboratory abnormalities for 2 months between hospitalizations. Prolonged PUO is also associated with noninfectious diagnoses, although tuberculosis may still be responsible. Empiric antituberculosis therapy had been considered for our patient before her final illness, given her ethnicity and travel history, but imaging failed to demonstrate a focus, and treatment was withheld. No evidence of tuberculosis was found on postmortem examination.

Suspicion of hematological malignancy led us to bone marrow examination. The elevated serum LDH level was nondiagnostic. In light of our negative results, a diagnostic splenectomy in the absence of splenomegaly would have been difficult to justify. Diagnosis can be difficult in patients with lymphoma who present with PUO if the lymphoma is intravascular or involves small bowel or bone, because results of bone marrow and CT scanning will be negative. Random skin biopsy of the trunk, thigh, or forearm has been shown to be helpful in the antemortem diagnosis of IVLBCL [9], even in the absence of definite skin lesions. Unfortunately, skin biopsies were not performed as part of our patient’s postmortem examination.

One other puzzling aspect about our patient was the dramatic clinical decline after the commencement of corticosteroids. This led to significant clinical concern about unmasked sepsis, despite extensive investigation. Corticosteroids are used as part of combination chemotherapy in the treatment of IVLBCL and have also been used for defervescence or to improve clinical performance status before chemotherapy [10]. Was her sudden and dramatic decline part of a cytokine storm from partial treatment of an aggressive and disseminated lymphoma?

Evaluation of a patient with PUO may be intensive and laborious, and definitive diagnosis may still remain elusive. IVLBCL should remain part of the differential diagnosis if lymphoma is considered as a possible diagnosis, and we recommend adding random skin biopsy to the list of suggested diagnostic tests.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References