SCIENCES

J Forensic Sci, 2016
doi: 10.1111/1556-4029.13101
Available online at: onlinelibrary.wiley.com

CASE REPORT

MEDICAL LIABILITY

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A Case of Lethal Idiopathic Plasmacytic Lymphadenopathy with Polyclonal Hypergammaglobulinemia: A Medical Challenge for the Forensic Pathologist*

ABSTRACT: A rare case of lethal idiopathic plasmacytic lymphadenopathy (IPL) with polyclonal hyperimmunoglobulinemia with chronic renal failure is described. A 40-year-old woman who had suffered from upper airways disease was admitted to the Emergency Room with acute renal failure and hypergammaglobulinemia. She developed pericardial effusion, a pruritic rash, splenomegaly and fell into a coma after 6 days. Multiple myeloma, infection, collagenopathy, and coagulopathy were ruled out. Finally, a form of malignant hypergammapathy was suspected. At autopsy, lymph nodes were infiltrated by polyclonal plasma cells and lymphocytes, with erythrophagocytosis features; immunohistochemistry confirmed the plasma cells (CD138+), with a prevalence of kappa-positive cells, B (CD20+) and T (CD3+) cells. Kidneys showed advanced glomerulosclerosis containing similar infiltrates. The cause of death was IPL with polyclonal hypergammaglobulinemia and advanced renal failure. Similar cases are unusual, and possible medical liability associated with failure to diagnose and treat idiopathic plasmacytic lymphadenopathy deserves discussion and further studies.

KEYWORDS: forensic science, autopsy, idiopathic plasmacytic lymphadenopathy, hypergammaglobulinemia, medical liability, histology

Idiopathic plasmacytic lymphadenopathy (IPL) was first described by Mori et al. in the early 1980s as a new disease type, similar to the plasma cell type disorder, Castleman's disease (CD). Both have multicentric lymphadenopathy, prominent polyclonal hypergammaglobulinemia, an elevated erythrocyte sedimentation rate, elevated serum interleukin-6 (IL6) concentrations, bone marrow plasmacytosis, and abnormal laboratory data such as anemia and positive autoantibodies. CD usually has an aggressive and fatal outcome associated with infectious complications or malignant tumors (1–4). IPL has a significantly better 5-year survival rate than CD but can be asymptomatic for a long time before exhibiting a rapidly fatal course due to an unexpected acute attack (4). This pathology is rarely recognized clinically and may be first diagnosed after the patient's death, even after admission to hospital, where prompt, successful treatment is expected. In this report, we describe the case of a patient admitted to hospital for acute renal failure and hypergammaglobulinemia, thought to be related to multiple myeloma. Several alternative diagnostic hypotheses were made, but no relief of the symptoms occurred despite the administration of therapy. The patient developed deep coma and died a few days later without a diagnosis; medical liability was suspected.

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*Presented at the 67th Annual Meeting of the American Academy of Forensic Sciences, February 16–21, 2015, in Orlando, FL.

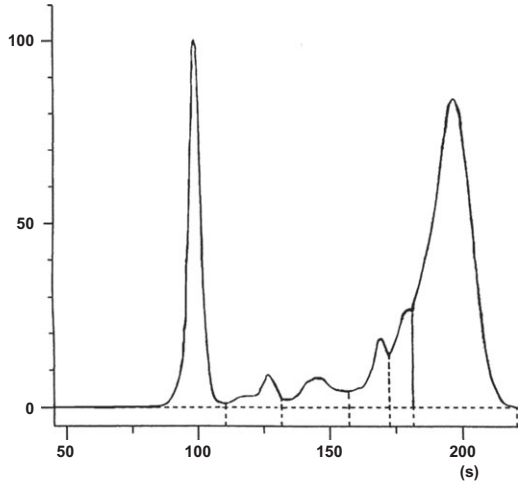
Received 18 June 2015; and in revised form 26 Oct. 2015; accepted 1 Nov. 2015.

Case History

A 40-year-old woman was admitted to the Emergency Room of a Southern Italy hospital with acute renal failure and hypergammaglobulinemia. She had a medical history of frequent otitis, pharyngitis, and poorly defined rheumatic disease. In the last month, she had been taking oral antibiotics, but she developed peripheral edema with initial renal failure, shown by biochemical tests, with high proteinuria, as well as polyclonal hypergammaglobulinemia at serum protein electrophoresis (Fig. 1). She was moved to the Hematology Unit with a diagnosis of multiple myeloma, but after 5 days she developed, in sequence, back pain, pericardial effusion, and a pruritic rash of the face and trunk with eyelid swelling, treated by analgesics and antihistamines. An enlargement of the spleen was detected, with nonpalpable liver and lymph nodes. Her blood pressure was high despite therapy. The respiratory function was normal. The next day she became hypothermic (after initial hyperthermia), disoriented, agitated, and confused with eye deviation; a brain hemorrhage was suspected, and the patient was moved to the Intensive Care Unit, where she was intubated. Thoracic computed tomography showed a posterior pleural effusion with partially collapsed lungs and interstitial thickening. On day 6 from admission, the patient became unconscious and then comatose; a lumbar puncture showed proteinorachia at 3035 mg/L, glycorrhachia

at 19 mg/dL, and numerous erythrocytes and mononuclear cells in the sediment. She underwent magnetic resonance imaging (MRI) with angio-MRI, which was normal except for nonspecific sinusitis. In the next few days, the Glasgow Coma Scale score decreased to 3. A full-body CT scan with contrast agent showed massive brain swelling and sinusitis, multiple subcentimeter axillary, supra clavicular and mediastinal lymph nodes, massive adipose tissue swelling of the thorax and abdomen, pericardial effusion, 17 mm thick, and left pleural effusion with a collapsed lung and interstitial thickening, splenomegaly, and signs of acute kidney failure.

At admission, the biochemical and serological tests had revealed renal dysfunction and an electrolytes imbalance. The diagnosis of multiple myeloma was ruled out because of the polyclonal pattern and the absence of bone lesions. Bone marrow survey showed 75% cellularity and polyclonal plasmacytosis. The first measurement of serum immunoglobulin (Ig) levels revealed the following values: IgG, 5933 mg/dL; IgA, 648 mg/dL; IgM, 946 mg/dL; kappa and lambda Ig light chains, 1283 mg/dL and 829 mg/dL, respectively, with no monoclonal values in urine, confirming the polyclonal pattern. The serological tests revealed anemia, low levels of leukocytes and lymphocytes with a normal platelet count. On the following days, the tests showed an increasing lymphocytopenia, thrombocytopenia, and leukocytosis with normal clotting parameters. Coagulative (such as thrombotic thrombocytopenic purpura) and collagen disorders were suspected, or else an infectious disease in view of the elevated levels of C-reactive protein, erythrocyte sedimentation rate, and procalcitonin, but these hypotheses were then ruled out, and the search for infectious agents was negative. Antibiotic and corticosteroid therapy was administered, but no relief of symptoms obtained. Of note, a further serum protein electrophoresis revealed a decrease of the total serum protein and hypergammaglobulinemia levels. While the additional suspicion of a hypergammaglobulinemia, symptomatic of a proliferative hematological disorder, had been raised, a multi-organ failure syndrome developed and the patient died 9 days after admission.



Indice	Banda	Area Rel.	Conc. (g/dl)	Intervalli
1	Albumina	22.65% B	2.49	54.70% ... 69.66%
2	Alpha 1	3.12%	0.34	2.63% ... 6.20%
3	Alpha 2	5.02%	0.55	4.87% ... 11.50%
4	Beta 1	5.79%	0.64	5.35% ... 9.19%
5	Beta 2	7.09%	0.78	2.38% ... 7.11%
6	Gamma	56.33% A	6.20	9.69% ... 18.90%
Totale			11.00	

FIG. 1—*Laboratory findings on admission.*

A forensic autopsy was requested to shed light on the cause of death and to exclude medical malpractice.

Autopsy Findings

The skin was rash-free. The brain showed massive swelling. The lungs were edematous with diffuse pleural adhesions. The heart was heavy (500 g) with concentric hypertrophy of the left ventricle. The spleen and liver were both enlarged (the spleen 350 g; the liver 1590 g); lymph nodes throughout the body were slightly enlarged. Both kidneys were pale and cystic, with no preservation of corticomedullary differentiation. Diffuse visceral congestion was also observed.

Toxicological analyses were unremarkable.

Microscopic Findings

Samples of the main organs were taken at autopsy, fixed in 10% formalin, and routinely processed by hematoxylin–eosin (H-E) staining and for immunohistochemistry. Lymph nodes showed diffuse infiltrates of plasma cells and lymphocytes, with erythrophagocytosis features (Fig. 2). Immunohistochemical staining confirmed the plasma cells (CD138+), with a prevalence of kappa-positive cells, B (CD20+) and T (CD3+) cells (Fig. 3*A–D*); expression of anti-apoptotic Bcl-2 protein and proliferation-related Ki-67 antigen was normal. The kidneys showed advanced glomerulosclerosis containing similar infiltrates and tubular protein cylinders, with massive sclero-hyalinosis (Fig. 4). Samples from the tongue and kidneys were negative at Congo red staining. An antemortem peripheral smear, obtained 2 days before death, showed rouleaux formations of red cells, moderate anisopoikilocytosis, and rare schistocytes.

These results confirmed that the cause of death was multiple organ failure, due to IPL with polyclonal hypergammaglobulinemia and advanced kidney failure.

Discussion

Idiopathic plasmacytic lymphadenopathy features clonal B-lymphocytes proliferation producing high levels of

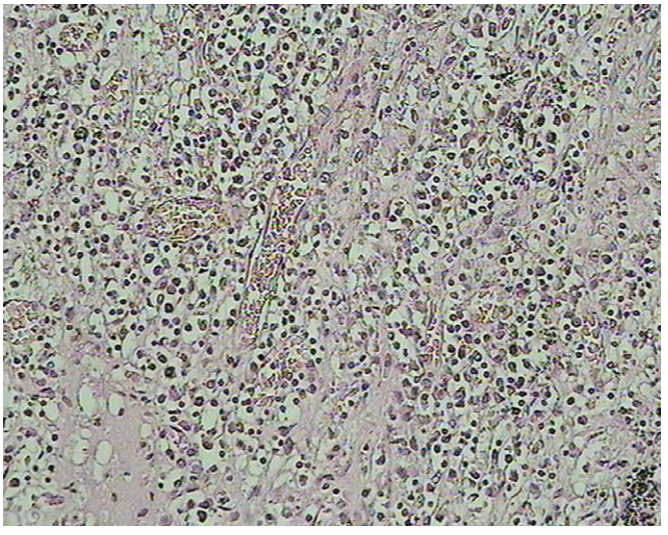


FIG. 2—*Microscopic examination of lymph nodes: diffuse infiltrates of plasma cells and lymphocytes with erythrophagocytosis features (H&E stain ×5 magnification).*

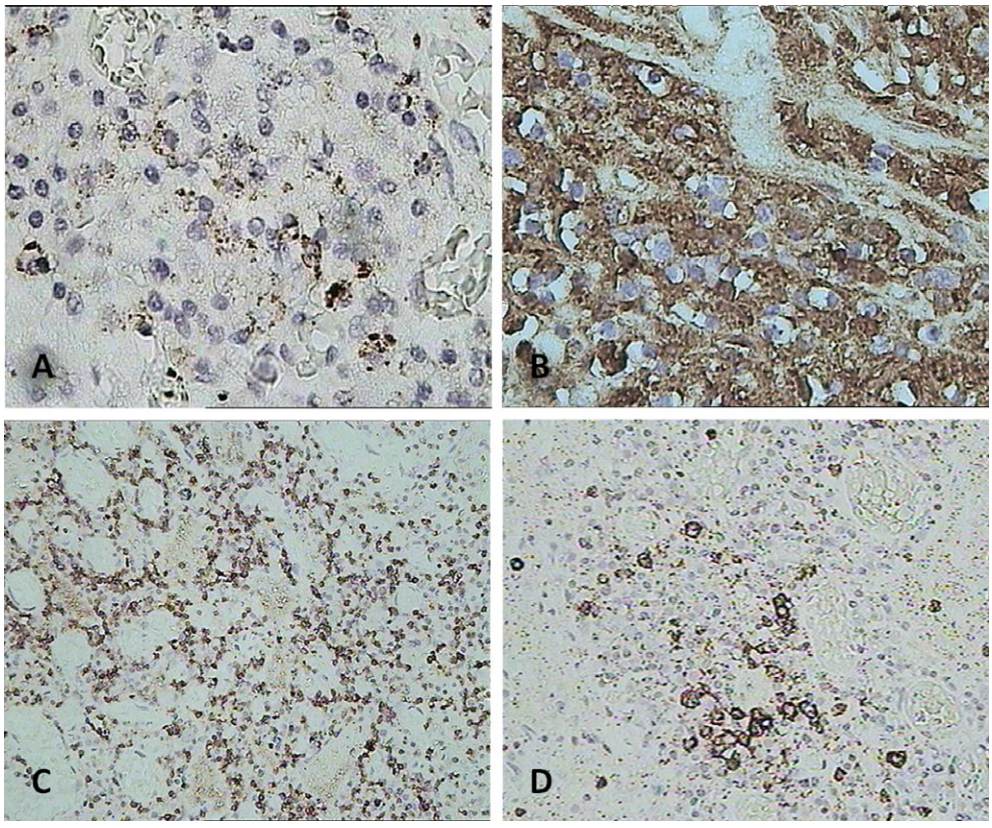


FIG. 3—*Immunohistochemical staining confirmed (A) the plasma cells with (B) a prevalence of kappa-positive cells, (C) cells type B, and (D) cells type T (CD138 – Kappa Chain – CD20+ – CD3+ Immunohistochemistry ×5 and ×20 magnification).*

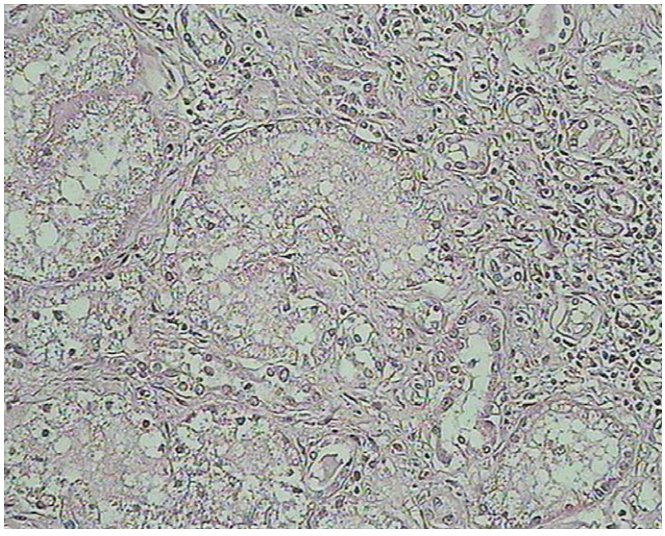


FIG. 4—*Microscopic examination of the kidneys showed advanced glomerulosclerosis containing similar infiltrates and tubular protein cylinders, with massive sclero-hyalinosis (H&E stain ×5 magnification).*

immunoglobulin and/or their chains, which affect the entire body. The clinical features are polymorphic because of the involvement of several organs (the skin, and pulmonary, digestive, and renal systems) (4–6). The treatment of IPL has not yet been established, but some authors have indicated the efficacy of corticosteroid treatment, anticancer chemotherapy, and monoclonal antibodies (7,8).

Even if ILP has been reported in literature, it is rarely recognized clinically and may be first diagnosed after the patient's death (9), disclosed by the forensic pathologist as medical examiner.

Mori et al. developed the following diagnostic criteria for IPL: (i) polyclonal hyperimmunoglobulinemia without M protein (Ig G exceeding 4500 mg/dL); (ii) systemic lymphadenopathy (>1.8 cm in diameter) with high plasmacytic infiltration but without deterioration of the basic structure; (iii) the exclusion of other diseases including infection, collagen, and autoimmune diseases, hepatitis and liver cirrhosis (7,10,11). The case described here fulfilled these criteria, and the diagnosis of IPL was formulated. Polyclonal plasmacytosis in bone marrow was also observed, a feature that frequently occurs in patients with IPL (1). Nevertheless, a differential diagnosis with other conditions in which bone marrow plasmacytosis may occur, for example, chronic inflammation, infectious, and autoimmune diseases, hypersensitivity, may be difficult (12).

Unfortunately, in the present case, the rapid worsening of the patient's condition did not allow the physicians to make a correct diagnosis, despite therapy. The case was particularly notable for the renal complications resulting from glomerulosclerosis and interstitial infiltration. Cases of fatal polyclonal systemic proliferations with renal failure are rare and have mostly been described by Japanese authors (3,8,13–15). The exact etiologic mechanisms of renal damage in IPL are unknown. It is thought that an overproduction of IL6 may induce proliferation of mesangial cells and interstitial infiltration of plasma cells into the renal interstitium, and these processes can be increased by paracrine or autocrine IL-6 production by mesangial cells and infiltrating plasma cells (3).

The occurrence of renal dysfunction should be considered, progressively worsening the patient's clinical course in IPL. In the present case, the renal damage resulted from glomerulosclerosis due to the infiltration of plasma cells into the interstitium, but the renal failure was refractory to corticosteroid therapy; this is the main therapy because it can contrast the overproduction of IL-6, inhibiting the release of pro-inflammatory cytokines (such as IL-6) by macrophages and T- and B-lymphocytes. Indeed, the therapy was actually effective in our patient, in terms of reducing the hypergammaglobulinemia, but no clinical improvement was observed.

In retrospect, the patient's initial clinical status (renal failure and hypergammaglobulinemia) could be highly suggestive of multiple myeloma, but the overlapping of a cutaneous rash and eyelid swelling led the physicians to consider an allergic or autoimmune disease. After a few days, deep neurological impairment was prevalent, mimicking a brain hemorrhage that was then excluded by CT scan and MRI. According to the changes of the clinical status, several diagnoses were considered but not supported by biochemical and serological tests and imaging, until death finally supervened.

In conclusion, IPL with polyclonal hypergammaglobulinemia is a rare entity that should be included in the differential diagnosis of several, more common pathologies (9). Nevertheless, this report stresses that all the findings from the clinical history examination, together with autopsy, must be interpreted with considerable caution. The forensic pathologist, as well as the hospital medical staff, must have an in-depth knowledge and a practical experience of such cases to avoid misinterpretations that could, in the worst cases, lead to a miscarriage of justice.

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