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## CASE REPORT

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# Sudden Unexpected Death Due to a Previously Undiagnosed Plasma Cell Dyscrasia

**ABSTRACT:** The plasma cell dyscrasias are a diverse group of disorders characterized by the production of a clonal paraprotein. Sudden death is a recognized complication of the plasma cell dyscrasias, most commonly in individuals with cardiac involvement by amyloidosis. However, the current forensic literature has no reported cases in which sudden death resulted from complications of a plasma cell dyscrasia that was first diagnosed by postmortem histologic examination. We present the case of a woman whose sudden and unexpected death resulted from a seizure. Postmortem examination revealed no evidence of trauma or a grossly identifiable natural disease process that would have accounted for her death. However, microscopic and immunohistologic studies revealed a previously undiagnosed plasma cell dyscrasia, the clonality of which was determined by immunohistochemical studies for immunoglobulin light chains, that was not associated with amyloid deposition. This case elucidates a previously unrecognized cause of sudden unexpected death and illustrates the importance of microscopic studies in selected cases examined in medical examiner/coroner offices.

**KEYWORDS:** forensic science, sudden death, microscopy, plasma cell dyscrasia

The dysproteinemias are diverse group of disorders that are associated with aberrant protein production. The majority of these disorders are classified as plasma cell dyscrasias, clonal proliferations of cells that have a plasma cell morphology and that produce a monoclonal serum and/or urine immunoglobulin and/or immunoglobulin fragment (1). Some of these disorders are clinically benign. Others, however, most notably multiple myeloma and Waldenstrom's macroglobulinemia, typically follow progressive and ultimately fatal courses and may be associated with morphologically malignant-appearing plasma cells (2). Plasma cell leukemia, which may arise as a *de novo* acute leukemia or as a terminal manifestation in the course of established multiple myeloma, is rapidly progressive (3–7).

Sudden death is a recognized complication of the plasma cell dyscrasias, most commonly in individuals with cardiac involvement by amyloidosis, which occurs in approximately 10% of patients with multiple myeloma (8,9). However, the current forensic literature has no reported cases in which sudden death resulted from complications of a plasma cell dyscrasia that was initially diagnosed by postmortem histologic examination. We have had the opportunity to study the case of a woman with only a vague past medical history of neurologic symptoms who of a seizure disorder of unknown etiology. Histologic and immunohistochemical studies performed on postmortem tissues revealed a previously undiagnosed plasma cell dyscrasia that was associated with the production of a monoclonal paraprotein.

### Case History

A 54-year-old woman with no known medical history other than an anxiety disorder and sinusitis was witnessed by her husband to have a seizure at home in 1994. She was transported to a local emergency room where a clinical neurologic examination and laboratory studies were unremarkable. An EEG was performed and was interpreted as a normal awake but drowsy EEG without epileptiform features. She was started on Dilantin and discharged with instructions to see a neurologist the following day. However, she was noncompliant with her seizure medication and did not see a neurologist until 2 years later when she presented with a 6-week history of recurrent episodes of upper extremity weakness, tinnitus, progressive hearing loss, and transient gait disturbances. Magnetic resonance imaging of the brain at that time showed abnormal leptomeningeal enhancement of the frontal, temporal, and parietal lobes, which was interpreted as suggestive of a malignancy, an infectious/inflammatory disorder or leptomeningeal fibrosis. A lumbar puncture was performed and revealed an elevated cerebrospinal fluid protein concentration. A monoclonal IgG lambda spike was identified by serum protein immunoelectrophoresis. The patient was encouraged to follow-up with a hematologic oncologist but failed to do so.

According to her husband, the patient was subsequently well until 2006, when she again sustained a seizure but did not seek medical attention. Approximately 1 month later, she had another seizure at home. Emergency Medical Services were called, but she was found in asystole and resuscitation efforts were unsuccessful.

The case was referred to the District 21 Medical Examiner's Office. The postmortem examination performed on the body of the 63 inch, 148 pound white female revealed no evidence of trauma or grossly identifiable natural disease process that would have accounted for her death. The brain was grossly unremarkable except for a focal area of leptomeningeal clouding over the right frontal lobe. Mild nephrosclerosis was the only other finding noted. No hepatosplenomegaly or lymphadenopathy was noted. Postmortem toxicologic studies were remarkable only for the presence of caffeine in the decedent's blood.

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Microscopic examination of the lungs revealed the presence of scattered bone marrow emboli (Fig. 1). The bone marrow emboli contained numerous mature-appearing plasma cells associated with scattered Russell bodies (Fig. 2). The spleen showed extensive, diffuse infiltration of the red pulp by plasma cells (Fig. 3). Unfortunately, no bone marrow had been retained at autopsy for histologic examination. Immunoperoxidase studies for kappa and lambda immunoglobulin light chains performed on sections of spleen and lung revealed immunostaining of the plasma cells in the spleen and bone marrow emboli for lambda light chains and the absence of immunostaining for kappa light chains. These findings indicated a monoclonal population of plasma cells. Sections of the meninges demonstrated diffuse fibrosis and the presence of focally calcified concretions, some associated with multinucleated foreign body-type giant cells (Fig. 4). Similar concretions were also scattered throughout the brain parenchyma. The Congo red stain performed on sections of the brain, meninges, and heart revealed no microscopic evidence of amyloidosis. Serum protein immunoelectrophoresis performed on postmortem blood revealed the presence of a monoclonal IgG lambda paraprotein. The cause of death was attributed to a seizure disorder complicating a previously undiagnosed plasma cell dyscrasia.

## Discussion

The sudden and unexpected death of an individual in whom the diagnosis of a potentially fatal disease has never been made is usually investigated by the office of the medical examiner or coroner. The majority of sudden unexpected natural deaths are due to cardiovascular causes, with coronary arteriosclerosis accounting for the largest proportion (10,11). Central nervous system causes of sudden unexpected deaths include neoplastic and infectious causes, as well as seizure disorders. The majority of seizure disorders are idiopathic in origin. Seizure disorders can result in death through either a single convulsion, status epilepticus, or by unknown mechanisms. The latter is termed "sudden unexpected death in epilepsy" (12–14). Less commonly encountered causes of sudden unexpected death include metabolic and endocrine disorders, such as diabetes mellitus and acute adrenal insufficiency. Although the cause of death in cases of sudden unexpected natural death can often be determined by gross autopsy findings alone, in some cases, most notably myocarditis, microscopic examination and ancillary studies may be essential in rendering the diagnosis.

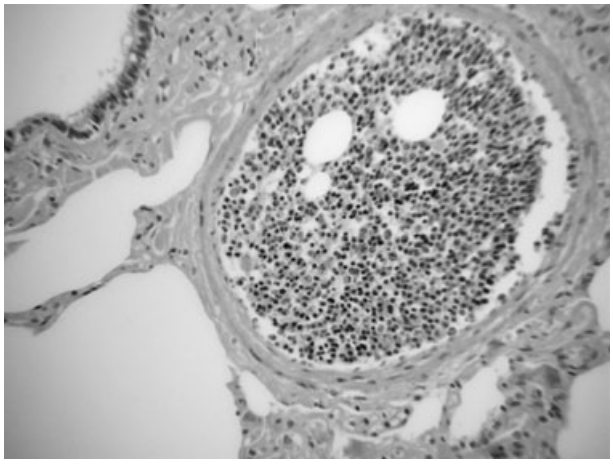

FIG. 1—*A section of lung showing a bone marrow embolus (H&E ×10).*

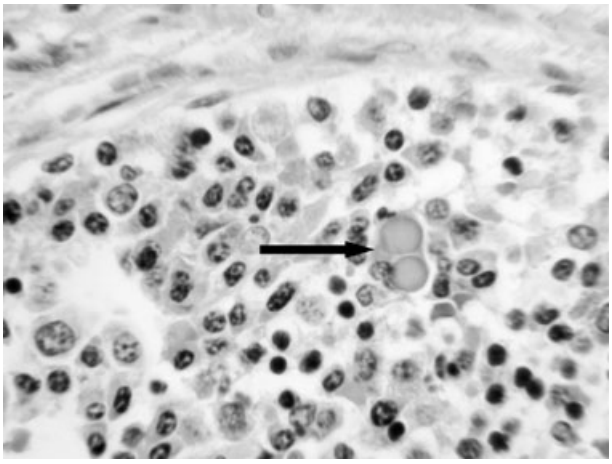

FIG. 2—*Higher magnification of a bone marrow embolus showing numerous plasma cells with scattered Russell bodies (arrow) (H&E, ×400).*

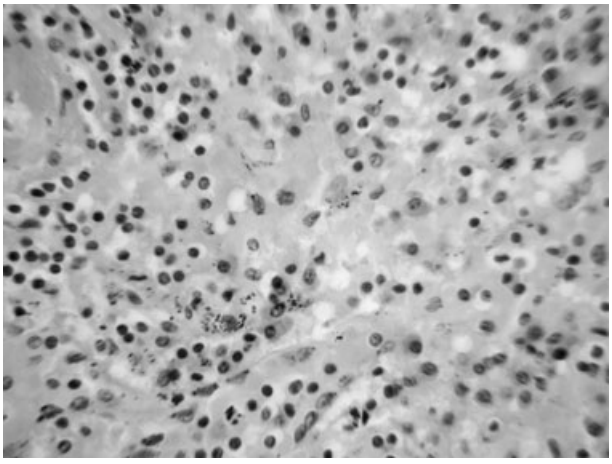

FIG. 3—*Diffuse infiltration of the red pulp of the spleen by mature-appearing plasma cells (H&E, ×200).*

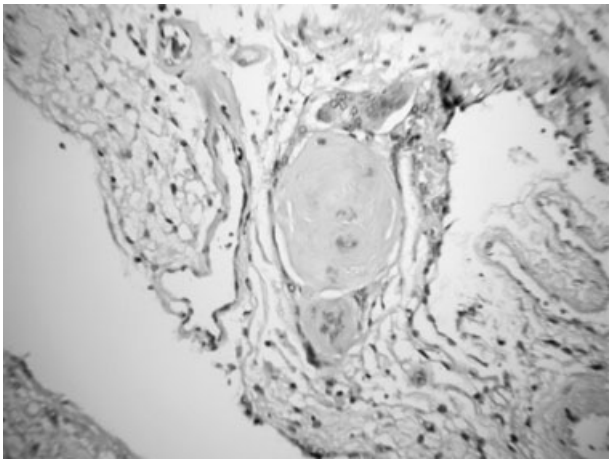

FIG. 4—*A section of the leptomeninges showing fibrosis and a focally calcified concretions surrounded by multinucleated giant cells (H&E, ×400).*

The dysproteinemias are a clinically and morphologically heterogeneous group of systemic disorders of the lymphoid system that are associated with the presence of abnormal proteins in the blood

(1). One subgroup, the autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, and Hashimoto's thyroiditis, is characterized by the abnormal production of antibodies, typically autoantibodies (1,15–19). In contrast, the plasma cell dyscrasias are associated with the production of a monoclonal, or occasionally biclonal, immunoglobulin, termed a paraprotein. The immunoglobulin production is aberrant because it occurs in the absence of a definable antigenic stimulation and is not self-limited (1). Some of the disorders appear histologically benign, while others show morphologic features of malignancy (2). Similarly, the behavior of these disorders varies from a benign or indolent clinical course to a rapidly fulminant and fatal one. A common histologic finding among these disorders is the presence of morphologic evidence of immunoglobulin production, including the presence of PAS-positive cytoplasmic and intranuclear immunoglobulin inclusions, termed Russell and Dutcher bodies, respectively. In some cases, amyloid deposition is identified (1,2).

The plasma cells dyscrasias are characterized by the production of monoclonal, or occasionally biclonal, paraproteins (1). Although the presence of a monoclonal paraprotein suggests a clonal, and therefore presumably neoplastic, proliferation, the dysproteinemias may be either morphologically benign or malignant-appearing histologically. Their clinical behaviors show a spectrum ranging from benign and nonprogressive to fulminant and rapidly fatal. The morphologically benign conditions include primary amyloidosis and some types of the heavy chain diseases, while the malignant-appearing disorders include multiple myeloma, Waldenstrom's macroglobulinemia and plasma cell leukemia, in addition to some non-Hodgkin's lymphomas of B-cell lineage (20–22).

Multiple myeloma, the most common of the plasma cell dyscrasias that follows a progressive clinical course, is a differentiating B-cell lymphoproliferative malignancy. The disorder is characterized by the unrestricted, monoclonal proliferation of plasma cells that may appear either histologically well-differentiated or overtly immature and malignant. Myeloma notoriously produces destructive skeletal lesions because of increased osteoclastic bone resportion and 30% of patients develops hypercalcemia, which is the most common metabolic complication of this disorder (9,23–26). Multiple myeloma may be associated with neurologic sequelae either as a direct result of infiltration of the central nervous system by the neoplastic cells or because of metabolic consequences including encephalopathy and/or seizures mediated by the hypercalcemia (8,27–29). Approximately, 10% of patients with multiple myeloma develops amyloidosis (8,9).

Myeloma typically follows a progressive and ultimately fatal course, with death most commonly resulting from infection because of bone marrow dysfunction and pancytopenia (30,31). However, sudden death is a rare complication of multiple myeloma and when present is usually due to the arrhythmias resulting from cardiac involvement by amyloid. Amyloidosis occurs in 80–90% of individuals with myeloma-associated amyloidosis (8). Skadberg et al. (32) reported the sudden death of a patient with multiple myeloma and cardiac amyloidosis who developed complete heart block. Plasma cell leukemia may arise either as a terminal manifestation in an individual with an established diagnosis of myeloma or as a *de novo* acute leukemia and typically follows the fulminant course characteristic of the other acute leukemias (3–7,33,34).

Our case is a highly atypical example of a plasma cell malignance that followed a very indolent course and was not diagnosed until postmortem examination was performed when the patient died 12 years after first exhibiting symptoms attributable to the disease. Histologic and immunohistochemical studies were crucial in determining the diagnosis. Although a peripheral blood smear was not available for examination, the pattern and the extent of involvement of the decedent's spleen at autopsy were consistent with plasma cell leukemia (1). Given the prolonged clinical course of the disease in this case, plasma cell leukemia most likely represented the leukemoid phase of multiple myeloma rather than a *de novo* malignancy. Although no premortem calcium levels were available to review, it is our hypothesis that the patient's seizures were the result of the hypercalcemia that frequently accompanies myeloma. This is supported by the finding of calcific deposits in the leptomeninges and brain parenchyma at autopsy that suggests metastatic calcification.

There has been recent controversy in the forensic literature pertaining to the value of histologic studies in medico-legal autopsies. Molina et al. (35) recently reviewed 189 forensic cases in which microscopic studies were performed. These investigators found that microscopic analysis affected the cause of death in only one case and did not affect the manner of death in any. Our case is an example of a situation in which the cause of death could only be determined through histologic examination. Although the performance of microscopic studies in all medico-legal cases would not be time efficient or cost effective, in certain cases microscopy is an essential part of the postmortem examination. As with all ancillary studies, it is incumbent upon the forensic pathologist to exercise judgment in determining which cases require microscopic examination for the determination of the cause and manner of death. Additionally, in selected cases microscopy may provide important information of potential public health significance, such as the presence of infectious disease processes, or may give family members the awareness of potentially inheritable conditions.

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