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CASE REPORT

PATHOLOGY/BIOLOGY

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Undiagnosed, Untreated Acute Promyelocytic Leukemia Presenting as a Suspicious Sudden Death*

ABSTRACT: Acute promyelocytic leukemia (APL) is a subtype of acute myelogenous leukemia frequently associated with clotting abnormalities and severe hemorrhagic diathesis. The disease is associated with a high incidence of early fatal hemorrhage. We report the sudden death of a 40-year-old male without significant medical history in which foul play had been initially suspected. A thorough postmortem investigation performed on the decedent lead to the diagnosis of APL. Cause of death was a cerebellar hematoma. Underlying APL should be considered in the differential diagnosis when unexplained bleeding is encountered in a decedent. This case emphasizes the value of routinely collecting bone marrow during an autopsy to enable accurate testing and diagnosis.

KEYWORDS: forensic science, forensic pathology, acute promyelocytic leukemia, sudden death, intracranial hemorrhage, differential diagnosis

The medico-legal literature often report cases in which an uncommon disease is undiagnosed during life or is misdiagnosed postmortem as foul play or abuse, including osteogenesis imperfecta, acute promyelocytic leukemia (APL), acute lymphoblastic leukemia, and Ehlers–Danlos syndrome (1–4). This report concerns a case of undiagnosed, untreated APL presenting as a possible homicide. We are reporting this case because of its rarity and to make forensic pathologists aware of the possible occurrence of this condition. We also emphasize the difficulty of the French forensic pathologist in assessing the cause of death in some cases because of the specificity of the French medico-legal system.

Case Report

A 40-year-old man was found dead in his short-term rental apartment by a colleague. He was a soldier in the Brazilian Army and was in France for a 3-week training period. He had a 2-month history of lower back pain, which was unsuccessfully treated with various anti-inflammatory medications. He had no other symptom, and a complete blood count and coagulation test were normal 1 month before his death. At the scene, law enforcement noticed multiple bruises of markedly different colors on the body. Although no breaking and entering was noted in the apartment, an autopsy was initially requested by the district attorney because foul play was suspected. At autopsy, the body weighed 76 kg and measured 180 cm in length. The external examination revealed brownish, reddish, yellow, and green subcutaneous hemorrhages on the torso as well as the upper and lower extremities. There was no visible head injury. The autopsy showed no subgaleal hemorrhage and no skull fracture. A diffuse, bilateral subarachnoid hemorrhage was present at the opening of the cranial vault. The brain weighed 1580 g and was fixed in formalin for histology. The heart weighed 394 g, and the coronary arteries showed minimal atherosclerosis. The lungs were moderately congested. The liver and spleen were enlarged and weighed 2600 and 284 g, respectively. There were no other remarkable findings. At the end of autopsy, meningitis was ruled out after a microbiological analysis of a dura mater fragment showing no abnormality. Toxicological analysis was negative for alcohol, illegal substances, and major prescription drugs. Neuropathology revealed a 4.0 cm right-sided cerebellar hematoma and intraventricular hemorrhage (Fig. 1). The Circle of Willis was intact. No intracranial arteriovenous malformation was found. The heart, lungs, kidneys, spleen, and liver were congested without any other microscopic abnormality. Histologic examination of the bone marrow was possible because the hyoid bone had been collected. The examination showed abnormal hematopoietic cells (Fig. 2). There was a proliferation of myeloid cells with an immature, apple-core nucleus, and heavily granulated cytoplasm (Fig. 3). Additional staining for myeloperoxidase revealed tumor cells, which were characteristic of APL. Immunoperoxidase stain showed no-stain for CD138, kappa and lambda light chains, CD34, CD117, CD15, or CD79a. The bone marrow was the only sample where such abnormalities were found. Death was attributed to intracranial hemorrhage because of APL and was ruled as natural.

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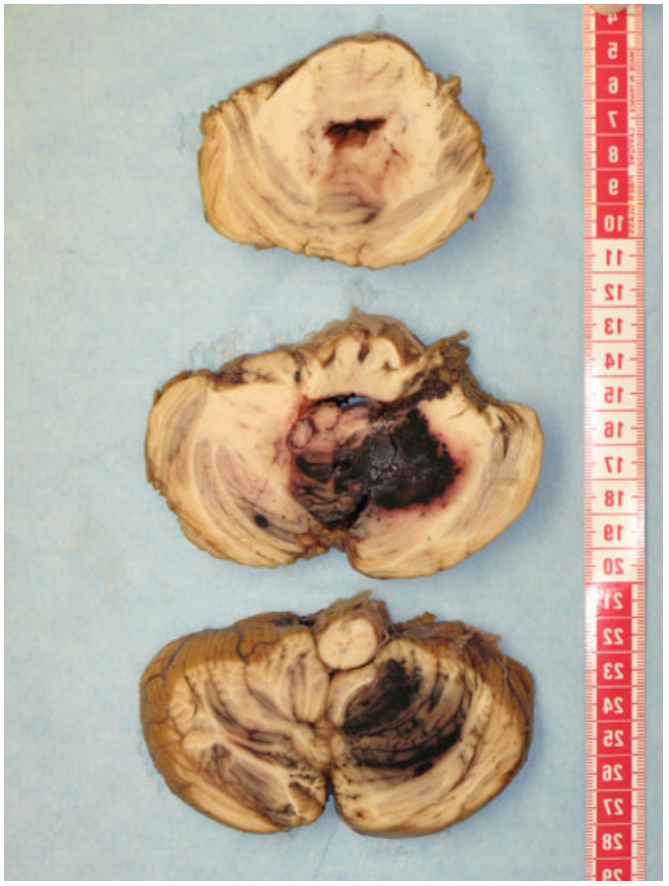

FIG. 1—*Coronal sections of the cerebellum showing a 4.0 cm right-sided hematoma.*

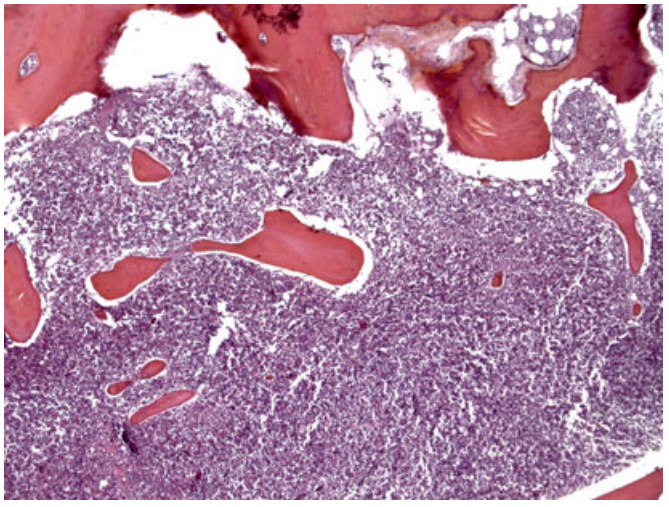

FIG. 2—*Low power view of the bone marrow showing a dense infiltration of the bone marrow and abnormal hematopoietic cells (×50).*

Discussion

APL is a subtype of acute myelogenous leukemia (5) and accounts for 10% of acute myeloblastic leukemias in adults (6). APL is characterized by the proliferation of abnormal immature myeloid cells and is classified as type M3 in the French-American-British leukemia system (7). It is associated with a nonrandom

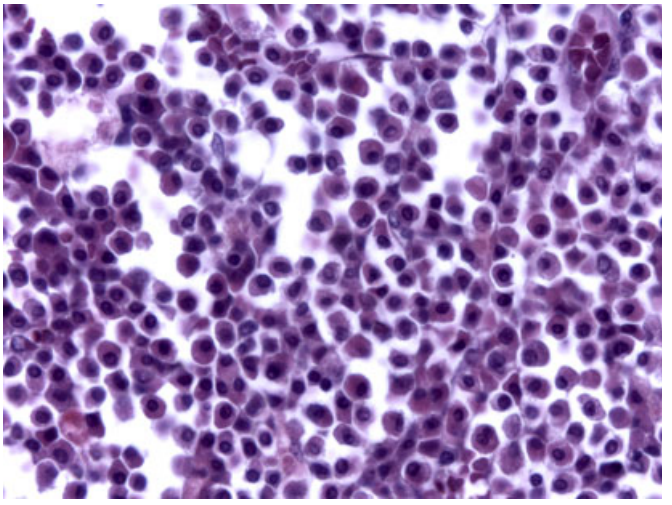

FIG. 3—*High power view of the bone marrow showing hypercellularity with an infiltration of abnormal promyelocytes with heavily granulated cytoplasm (×640).*

chromosomal abnormality characterized by balanced reciprocal translocations between the long arms of chromosomes 15 and 17 (6). APL is unique among leukemias as complete remission can be achieved with all-trans-retinoic acid treatment (6), without requiring marrow aplasia (5). However, APL is regarded as a medical emergency because of associated life-threatening hemorrhage (8). Sakai et al. (2) reported the case of a 15-year-old boy with no significant medical history who died within 12 h of presentation because of a cerebral hemorrhage caused by underlying APL. At autopsy, the brain showed hemorrhage at the right putamen in the basal ganglia, accompanied with ventricular rupture; the diagnosis was made on histology of the bone marrow. Early mortality is frequent, primarily from intracranial hemorrhage (6). The incidence of death because of fatal hemorrhagic complications is estimated to be 10–30% of the patients. While it is stated than an initial leukocyte count greater than 4×10^9/L and a platelet count less than 20×10^9/L are associated with an increased risk of intracranial hemorrhage and with death within 24 h (9), the blood count can also be normal at diagnosis (10). Mechanisms involved in hemorrhagic diathesis are hyperfibrinolysis, thrombocytopenia (6), and disseminated intravascular coagulation resulting from the release of procoagulants from abnormal promyelocytes (5,11). APL patients presenting with uncommon symptoms or diseases such as pseudotumor cerebri (12), granulocytic sarcoma (9), postpartum hemorrhage (13), or pulmonary complications (14) have been described. According to the literature, leukemias in general are among the most common undiagnosed neoplasias that cause sudden and unexpected death in adults with bronchogenic carcinoma, gastric adenocarcinoma, and adenocarcinoma of the urinary bladder (15). These situations usually raise suspicion of foul play, and an autopsy is often performed to rule out homicide.

The French medico-legal system is inquisitorial in nature. In France, the decision to perform additional analysis after an autopsy is made by the district attorney and not by the medical examiner. Histopathology and toxicology are not automatically performed, which can be explained by the fact that the district attorney, and not the medical examiner, is the one who determines the mode of death. This can lead to difficult situations where the pathologist thinks histology or toxicology should be performed, but the district attorney disagrees, frequently for cost-related reasons. The main concern of the

authorities is to rule out homicide. The determination of cause of death is not a priority to the authorities if the autopsy results are consistent with natural, accidental, or suicidal death. In our case, circumstances of death and external examination of the body did not raise the diagnosis of a malignant neoplasm in the hematopoietic system. The diagnosis of the disease could have been easily overlooked, as the victim presented with multiple bruises that seemed consistent with injuries. Histology and toxicology were requested by the district attorney not only because of the numerous bruises on the body, but also because of the sensitive nature of the case due the profession of the decedent. This case also demonstrates the importance of collecting bone marrow in a routine manner to allow further testing and diagnosis confirmation if requested.

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