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CASE REPORT

Sudden death due to undiagnosed acute promyelocytic leukemia: a case report

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Abstract Acute promyelocytic leukemia (APL) is associated with severe hemorrhagic coagulopathy induced by the release of procoagulant, plasminogen, and protease from leukemic cells. The case described in this report is of a 15-year-old male who unexpectedly died due to a cerebral hemorrhage caused by underlying APL within 12 h after presentation. This case suggests that underlying APL should be considered as a differential diagnosis when sudden death occurs with a fatal spontaneous hemorrhage, although it is rare.

Keywords Sudden death · Acute promyelocytic leukemia · Hemorrhagic diathesis · Cerebral hemorrhage

Introduction

Acute promyelocytic leukemia (APL) is a hematologic neoplasm characterized by the potential for fatal hemorrhagic complications due to disseminated intravascular coagulation (DIC) and fibrinolysis, compared to other subtypes of acute myeloid leukemia in the French–American–British (FAB) classification [1–4]. The incidence of death due to fatal hemorrhagic complications with APL is estimated to be 10–30% of the patients [4–6]. At present, untreated cases in APL are rare [7]; therefore, the main clinical concern with APL appears to be the prevention of the fatal hemorrhages during remission induction therapy [1, 4, 5, 8–12]. This report describes the case of a boy who unexpectedly died after a short period of time from the onset of symptoms and was identified postmortem as an undiagnosed APL patient.

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Case report

A 15-year-old boy with no significant personal and family medical history was found in cardiopulmonary arrest at 8:50 A.M. in his bed by a family member. Because paramedics identified him as dead on arrival, they did not transfer him to a medical facility. According to his family, he was physically fit and had practiced the martial art, "karate", for years. Seven days before his death, while intervening in a fight between classmates, he was slapped in the face two or three times. The slaps only caused a slight headache that improved within a few days. After this event, he did not have any particular health complaints and regularly practiced karate. However, the night before his death, he complained of a fever (approximately 39°C), sweating, general weakness, loss of appetite, and urinary incontinence, and went to sleep at midnight without dinner. The next morning, the family found him with froth at the nose and lying facedown on his bed, unresponsive.

Autopsy findings

Because the cause of death was unknown, a forensic autopsy was performed 12 h after death. In the external examination, considering his age, the body was well-built

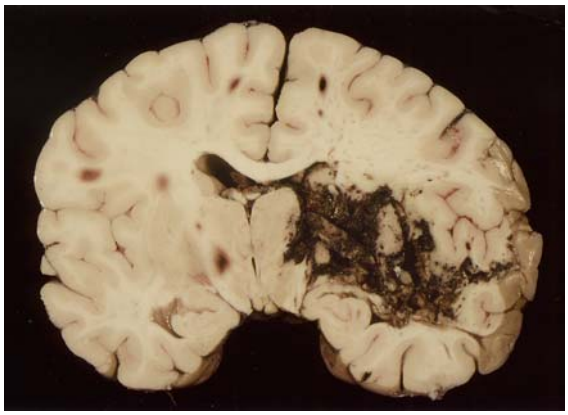

Fig. 1 Coronal slice of the brain at the level of the basal ganglia showing cerebral hemorrhage in the right putamen with ventricular rupture

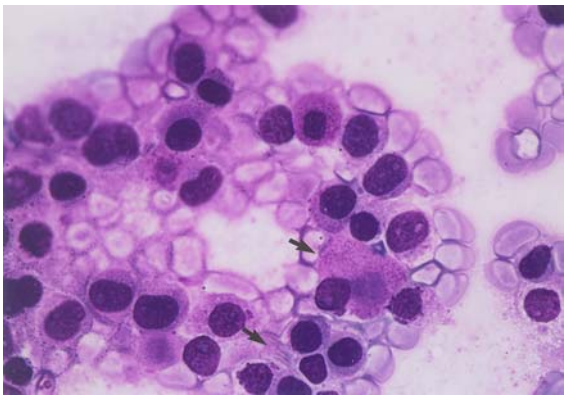

Fig. 3 Proliferated promyelocytes containing a number of azurophilic granules and Auer rods (*arrows*) in the blood smear from lumbar (Giemsa, ×800)

(weight 97 kg, height 171 cm, body mass index 32.9 kg/m^2), and multiple subcutaneous hemorrhages were observed in the face, on the front of the trunk and both upper and lower limbs, varying in size from 2×1 cm in the right femur to 9×7 cm in the left forearm. By the internal examination, the intercostal muscles, anterolateral cervical muscles, diaphragm had intramuscular hemorrhages. The brain presented excessive hemorrhaging at the right putamen in the basal ganglia with a ventricular rupture, which displaced the right thalamus to the left (Fig. 1). Also, there were small scattered hemorrhages in the subcortical white matter, which were also identified in other tissues such as the lungs, pericardium, and myocardium. Grossly, the lumbar bone marrow was sludge-like and less reddish and the hyperplastic tissues were bulging out from the surface of the section. The liver and spleen were enlarged weighing 1,755 g and 300 g, respectively. The kidneys were anemic (left weight 155 g, right weight 150 g) and hemorrhagic masses of approximately 2.5×2.0 cm were observed in the renal medulla. The gastrointestinal tract had no remarkable findings except for slightly anemic serosa and mucosa.

Histologic examination

In the histologic examination, the bone marrow from lumbar showed a diffuse neoplastic proliferation of myeloid cells and almost no normal hematopoietic cells (Fig. 2). Also, the blood smear presented a number of abnormal promyelocytes with a low nucleus to cytoplasmic ratio that contained numerous azurophilic granules and Auer rods in the cytoplasm, which is a morphological characteristic of acute promyelocytic leukemia (Fig. 3). Because only a few samples of blood smears and bone marrow were taken at autopsy, specific stains, such as myeloperoxidase and leukocyte specific esterase, were not implemented. Furthermore, proliferated leukemic cells were found in non-hemopoietic tissues of the brain, myocardium, lungs, liver, spleen, kidneys, and skeletal muscles such as the intercostal muscles and diaphragm (Fig. 4). In the spleen, extramedullary hematopoiesis occurred with colonies of erythroblasts and myeloblasts. In addition, the lung tissue was edematous and the major organs were generally anemic.

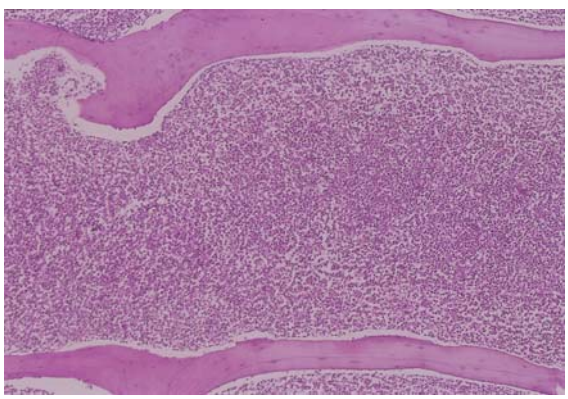

Fig. 2 Micrograph of bone marrow showing a neoplastic proliferation of myeloid cells (hematoxylin and eosin, ×25)

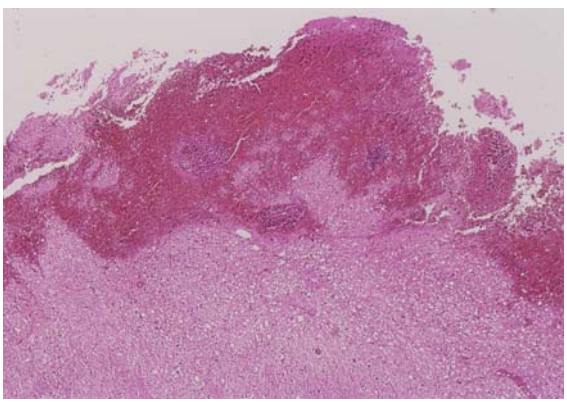

Fig. 4 Micrograph of cerebral hemorrhage with invasion of leukemic cells (hematoxylin and eosin, ×25)

Cause of death

Death was attributed to cerebral hemorrhage caused by hemorrhagic diathesis due to acute promyelocytic leukemia; the manner of death was stated as natural.

Discussion

APL is distinguished from other subtypes of acute myelocytic leukemia based on the morphology, cytogenetics, and clinical presentation. Morphologically, APL is classified as an M3 (hypergranular type) or M3 variant (hypogranular type) with increased abnormal promyelocytes and multiple Auer rods according to the FAB criteria [13]. The cytogenetical characteristic is a balanced reciprocal translocation between chromosome 15 and chromosome 17 that forms PML-RARαfusion gene, which encodes a PML-RARα protein to inhibit differentiation of promyelocytes [14, 15]. In the clinical presentation of APL, fatal bleeding due to hemorrhagic diathesis is a specific characteristic compared to other types of leukemia [1–6]. Although the mechanism of bleeding coagulopathy has not been entirely explained, it is considered to result from disseminated intravascular coagulation (DIC), fibrinolysis, and proteolysis caused by procoagulant, plasminogen activator, and protease released from abnormal leukocytes [2, 4, 6]. If chemotherapy is implemented to treat APL, the hemorrhagic diathesis can be exacerbated by the effect of cytotoxicity with destruction of the leukocytes [2, 5, 14, 16]. Because fatal hemorrhagic events due to hemorrhagic diathesis, mainly cerebral hemorrhages, have impaired the survival rate of APL, prevention of hemorrhagic death is a substantial issue in the management of APL patients [1, 4, 5, 8–12]. However, undiagnosed APL has been infrequent in recent decades and the development of a treatment for APL with all-*trans*-retinoic acid has decreased the number of hemorrhagic events [3, 5, 7, 17]. Therefore, most studies of APL have reported the analyses of sudden death during induction therapy [5, 11, 18], while it is still expected that a certain percentage of patients with APL could suddenly die before the diagnosis.

Also, because the most common causes of sudden natural death in childhood and adolescence are infectious diseases and cardiovascular abnormalities [19, 20], hematologic malignancies are not frequently considered as a differential diagnosis. In fact, half of pediatric sudden deaths are caused by previously diagnosed conditions such as epilepsy, cardiovascular abnormalities, and asthma. In sudden deaths caused by abnormalities discovered at autopsy, 90% of them are attributed to infectious diseases and cardiovascular abnormalities [21]. In this case, the process of death and external examination at the autopsy did not actively raise the diagnosis of a malignant neoplasm in the hemopoietic system until the internal examination and the histologic findings revealed the excessive bleeding consistent with hemorrhagic diathesis due to DIC in APL.

In conclusion, this report shows the likelihood of encountering a patient with undiagnosed APL underlying the major cause of death, such as a cerebral hemorrhage. APL may be considered as a differential diagnosis of sudden death with severe bleeding in major organs, although it is rare. When APL is suspected from the hemorrhagic features in clinical profiles or autopsy findings, a sufficient number of samples from blood and bone marrow should be removed at autopsy to confirm malignant neoplasms in the hemopoietic system and to differentiate this from other subtypes of leukemia.

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