Unexpected sudden death due to acute myeloid leukemia subtype M5: a case report and review of the literature

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Abstract: Acute myeloid leukemia (AML) is one of the most frequent myeloid malignancies. In patients with the disease, death often occurs due to complications of marrow failure, such as sepsis or significant hemorrhage. Rarely, undiagnosed and rapid evolving cases may present with fatal multi-organ failure. The authors report a case of sudden death in a 67-year-old woman who had been in apparent good health. A thorough post-mortem investigation performed on the decedent led to the diagnosis of acute myeloid leukemia subtype M5. Autopsy and histopathologic findings allowed us to determine AML complicated by multiple organ failure as the cause of the death. The case report suggests that underlying acute myeloid leukemia should be included in the differential diagnosis of sudden death with multisystem organ failure, however rare. Actually, it represents a quite unusual cause of sudden death, rarely reported in the medicolegal literature. A complete forensic approach by means of autopsy, histological and immunohistochemical analyses is deemed essential in order to correctly determine both the cause and the mode of death.

Key Words: Sudden death, acute myeloid leukemia, multisystem organ failure, immunohistochemical analyses.

Acute myeloid leukemia (AML) is a hematological neoplasm characterized by the clonal expansion of myeloid blasts in peripheral blood, bone marrow and other tissues [1, 2]. In this type of cancer, blasts characteristically lose their ability to differentiate normally and to respond to regulators of cellular proliferation that lead to the eventually fatal complications of infection, bleeding or organ infiltration, in the absence of treatment, within a year of diagnosis [3, 4].

The French-American-British (FAB) classification system divides AML into eight subtypes based on the cell type from which the leukemia develops and its degree of differentiation. The 4th edition of the WHO classification includes other prognostic factors, such as molecular markers and chromosome translocations along with the diagnostic criterion of a myeloid neoplasm with 20% or more blasts in peripheral blood smears or bone marrow aspirates [5]. Known risk factors for AML include smoking and exposure to ionizing radiation or certain chemicals, such as benzene or petrochemicals and presumably pesticides. Whether or not such exposures actually result in AML may reflect variations in the activity of enzymes, such as occurs in NAD(P) H:quinone oxidoreductase 1 (NQO1) gene polymorphisms, responsible for the metabolism and detoxification of carcinogenic substances [6].

Moreover, therapy-related AML (t-AML) is a recognized clinical syndrome occurring as a complication after cytotoxic and/or radiation therapy for solid tumors or hematologic cancer. Foremost among the t-AMLs is the one following therapy with alkylating agents (cyclophosphamide, ifosfamide, mechlorethamine, melphalan, busulfan, nitrosureas, chlorambucil, dacarbazine, and platinum compounds). Less frequently, t-AML follows therapy with topoisomerase II inhibitors (epipodophyllotoxins and anthracyclines).
or antimetabolites, such as fluorouracil, methotrexate, 6-mercaptopurine, and fludarabine, etc [7, 8]. Standard treatment of AML consists in aggressive chemotherapy, frequently achieving complete remissions, whereas it tends towards rapid progression when left untreated.

Our report focuses on a case of previously undiagnosed, untreated AML presenting as a sudden and unexpected death. We report the case in an attempt to heighten the awareness of forensic pathologists to the possibility of its occurrence, besides deeming it noteworthy for its rarity.

**CASE REPORT**

A 67-year-old woman in apparently good health and with no history of disease or known malignancy died of unknown causes in the emergency room at the Hospital of Genoa (Italy). The woman had been employed in a clothes shop. On the day prior to her death she reported having had continuous diarrhea and vomiting, in the preceding several days, to her primary care physician and was treated with antiemetic and antidiarrheal therapy and rehydration.

The autopsy was performed 24 hours after death and blood and organ samples were collected to perform microscopic and immunohistochemical examinations. Her weight and height were 48 kg and 160 cm, respectively. Lividity was evident posteriorly and partially fixed. External examination showed numerous purplish ecchymoses involving the entire body, especially the infra-mammary regions, abdomen and limbs, initially presumed to be post-traumatic in nature (Fig. 1).

At autopsy the woman’s heart, which demonstrated normal coronary arteries with no presence of obstructive disease, weighed 295 g and, macroscopically, the myocardium and heart valves presented no significant alterations. Her left and right lungs weighed 650 g and 730 g, respectively, whereas her brain weighed 1.430 g.

Moreover, on gross examination organs of the chest and abdomen appeared pale. Her liver weighed 1,800 gr, was firm in consistency and had an irregular surface with multiple nodular formations (Fig. 2) ranging in size from a few mm to 2 cm, whitish and hard-elastic in consistency. Both adrenal glands were increased in volume due to the presence of large masses, approximately 4 x 3 cm, elastic in consistency and grayish in color. The autopsy also revealed cerebral edema and mild pulmonary congestion. Microbiological analysis excluded infections and sepsis.

Histopathologic analysis (Figs 3, 4) performed on tissues samples confirmed extensive infiltration by neoplastic hematopoietic cells in liver, kidney, brain, heart, lungs, pancreas, and spleen vessels. On immunohistochemical evaluation (Fig. 5), the neoplastic elements were weakly positive for CD45 expression, with focal positivity for CD 68/KP1, CD68/PGM1 and Myeloperoxidase. No CD 34, CD 20, CD 3, CD 117, or CD 30 expression was observed. Moreover, quantitative growth fraction evaluation with monoclonal MIB-1 was significantly high. Thus, the multiorgan neoplastic infiltration was confirmed to have the immunohistochemical profile of AML subtype M5 or acute monocytic leukemia. Additionally, histological examination showed alveolar pulmonary edema, brain congestion and perivascular edema.

Further testing excluded any polymorphism in NAD(P)H:quinone oxidoreductase 1 (NQO1). Consequently, a thorough forensic approach comprehensive of autopsy and histological and immunohistochemical analyses led to the conclusion that death was caused by multiple organ failure (MOF) secondary to AML (FAB) M5.

**DISCUSSION**

AML is the most common of the myeloid malignancies, with an incidence of 3.8 cases per 100,000, which increases with age reaching 17.9 cases per 100,000 adults aged 65 years or older [4-9].

Most AML is associated with somatically acquired mutations, which inhibit terminal myeloid differentiation. Therefore, normal bone marrow elements are replaced with undifferentiated blasts expressing one or more phenotypes of the early phases of the myeloid lineage [10].

Cytogenetic aberrations can be demonstrated in approximately 50% to 60% of adult cases [11]. The majority of cases show recurrent balanced translocations. This subset of prognostic factors predicts resistance to, at least, conventional therapy, hence response to induction therapy and ultimately survival [3].

FAB subtype M5 or acute monocytic leukemia represents 10% of all cases of AML. Clinically, the disease is associated with hyperleukocytosis, extramedullary involvement, and coagulation abnormalities including disseminated intravascular coagulation [12]. This subtype shows a positive CD68/KP-1, CD68/PGM1 and myeloperoxidase (MPO) with a contemporary non-expression of CD34 and CD20, CD3 [13].

Characteristically, in symptomatic AML patients the presentation is non-specific with fatigue, hemorrhage, or infections and fever. Pallor and dyspnea on exertion are also common. Nevertheless, these are accompanied by varying degrees of anemia, thrombocytopenia with high, normal, or low white cell counts on complete blood counts, abnormal coagulation profiles, especially disseminated intravascular coagulation (DIC) and, usually, circulating blasts in peripheral blood smears and, occasionally, schistocytes, if DIC is present [14].

Furthermore, in AML-M5 there is a high incidence of bleeding disorders and leukemic infiltration of various tissues, manifesting clinically as hepatomegaly,
splenomegaly, leukemia cutis (skin), lymphadenopathy, bone pain (bone), gingival hyperplasia and neurological signs and symptoms (central nervous system).

A timely antemortem diagnosis of AML is based on the morphologic identification of leukemic myeloblasts in preparations of peripheral blood and bone marrow using a May-Grunwald-Giemsa or a Wright-Giemsa stain. Subsequent analysis is required to distinguish AML from acute lymphoblastic leukemia (ALL) by showing evidence for commitment to the myeloid lineage. Immunohistochemical staining for myeloperoxidase is the method of choice for identifying cells committed to the myeloid lineage. Since the leukemic clone may arise at any point of differentiation of the myeloid cell line, AML can be heterogeneous among patients. Flow cytometry and cytogenetics then serve to differentiate the various AML subtypes. According to the widely used WHO criteria a threshold of 20 percent leukemic blasts in a bone marrow aspirate is diagnostic of AML, whereas patients

Figure 1. External examination. Autopsy highlights on whole body surface numerous small purplish ecchymosis-like spots and bruising.

Figure 2. Autopsy findings. Internal examination revealed small, yellowish-white, firm and diffuse hepatic nodules.

Figure 3. Histological findings. Histopathologic analysis performed on the tissue samples confirmed the presence of neoplastic hematological cells in brain (A), heart (B) lung (C) and kidney (D). H&E, x 60.

Figure 4. Histological findings. Histopathologic analysis of liver. (A) H&E, x 2, (B) H&E x 4, (C) H&E x20. Neoplastic nodules and infiltration of periportal. (D) Cytology. Medium-sized cells. Large and eosinophilic cytoplasm. H&E x 60.

Figure 5. Immunohistochemical findings. Immunohistochemistry showed neoplastic elements with focal positivity for Myeloperoxidase (A), weak positivity for CD45 (B) and focal positivity for CD68/PGM1 (C) and CD 68/KP1 (D).
with recurring cytogenetic abnormalities are classified as having AML regardless of blast percentage [15, 16]. The postmortem diagnosis is often challenging, requiring careful and thorough autopsy and histological examination in order to identify the neoplastic origin and define its characteristics. Untreated AML has a rapid organic diffusion, thus an accurate histological and immunohistochemical examination of tissue infiltrates, inevitably present in such cases, usually allows us to trace the cause of death, identifying the neoplastic subtype for the confirmation and differential diagnosis of AML.

Bone marrow failure (infection and haemorrhage) is the leading cause of death, with the majority of patients succumbing before developing overt AML [17]. Less frequently, death may result from multiple organ failure (MOF). In addition, sudden death due to hemorrhagic complications is especially common in the acute promyelocytic leukemia (APL) subtype of AML. In such patients the incidence of death due to fatal hemorrhagic complications is estimated to be 10–30% [18, 19].

For instance, Sakai et al. [20] describe a case of sudden death due to an undiagnosed APL. At autopsy the 15-year-old boy was found to have cerebral hemorrhage in the right putamen with ventricular rupture caused by the hemorrhagic diathesis typical of these leukemias.

Similarly, San-Martín et al. [21] describe the case of a 40-year old man with no history of disease who died under apparently suspicious circumstances. Autopsy findings revealed cerebellar hemorrhage, while histologic and immunohistochemistry analyses confirmed an unsuspected and untreated APL. Therefore, death was attributed to intracranial hemorrhage with APL as the underlying cause.

In contrast, sudden death due to multiple organ failure (MOF) resulting from acute leukemia is quite rare. In the medicolegal literature there is a single described case [22] of a 60-year-old patient with fulminant MOF, leukopenia, thrombocytopenia, splenic infarction and normal peripheral smear. An autopsy showed a massive infiltration of Leukemic cells involving various organs. In the case we report herein, the history revealed non-specific symptoms. In addition, there were no known environmental or genetic risk factors and the woman had not been taking anticancer treatments associated with secondary, i.e. treatment-related, AML. However, the presence of ecchymoses throughout the body raised the suspicion of a blood clotting defect compatible with leukemic disease, although the lesions could have resulted from trauma. In the latter, lesions originate from microvasculature rupture, whereas non-traumatic ecchymoses are due to thrombocytopenia of marrow failure and/or DIC. Indeed, in the absence of a timely diagnosis of AML and treatment, it rapidly underwent extensive dissemination, up to the point of multiorgan failure. The diffuse neoplastic infiltration caused activation of cytokines and production of vasoactive and proinflammatory mediators. Results of immunohistochemical analyses allowed us to confirm the diagnosis of AML M5, which often results in extensive extramedullary disease if not treated promptly.

CONCLUSION

AML is one of the most frequent myeloid malignancies with an incidence of 3.8 cases per 100,000. Death is almost always related to bone marrow failure that leads to infections and bleeding, while multi-organ failure is quite rare. The case presented is an unusual cause of sudden death, rarely reported in the literature. A complete histological and immunohistochemical investigation accompanied by the necessary forensic investigation are deemed indispensable in order to correctly determine the cause of death and identify the pathologic mechanism.

In conclusion, acute myelogenous leukemia should be considered in all patients presenting with unexplained multiorgan failure.

Conflict of interest. The authors declare that they have no conflict of interest concerning this article.

References