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A rare case of aCML associated with CNS involvement and with aggressive clinical course

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ABSTRACT

The presence of neutrophilic leukocytosis may underlie a wide variety of diseases. Some rare causes of neutrophilia might be chronic neutrophilic leukemia (CNL) and myelodysplastic/myeloproliferative neoplasm with neutrophilia (MDS with neutrophilia). Here we report a case of a 78-year-old woman who came to our ER due to severe leukocytosis and anemia on a routine check-up. The patient was asymptomatic and the last exams available showed a mild leukopenia and thrombocytopenia. The abdominal echography showed mild splenomegaly The patient underwent bone marrow (BM) examinations. One week later, the patient presented mental deterioration. The patient underwent a cranial CT and RMN that showed multiple lesions of 11 mm in the brain parenchyma, cerebellum and encephalic trunk. Another week later, the clinical presentations worsened: she was in a comatous state and feverish 40 °C unresponsive to steroid therapy. Autopsy showed a leukemic and hemorrhage infiltration in multiple organs and in the BM a cellularity of 100% represented by myeloid elements with a slowdown maturation with blasts 5%. According to WHO 2016 this case can be reported as an aCML, an MDS/MPN overlap syndrome that is difficult to differentiate from a CNL.

1. Introduction

Neutrophilic leukocytosis encompass a broad range of hematologic and non-hematologic disorders. An accurate diagnosis requires the exclusion of potentially confounding entities such as reactive neutrophilia/ leukemoid reaction, chronic neutrophilic leukemia (CNL), chronic myeloid leukemia (CML), neutrophilic-CML (CML-N), and myeloproliferative neoplasm/myelodysplastic (MPN-MDS) overlap disorders such as myelodysplastic/myeloproliferative neoplasm with neutrophilia and chronic myelomonocytic leukemia (CMML), as well as other myeloid neoplasms.

Chronic neutrophilic leukemia (CNL) and myelodysplastic/myeloproliferative neoplasm with neutrophilia (MDS/MPN with neutrophilia) are rare hematologic neoplasms that are characterized by leukocytosis and hypercellularity of bone marrow (BM) consisting predominantly of granulocytic cells, the absence of the Philadelphia chromosome with translocation t(9;22) (*BCR-ABL1*) and other myeloid driver mutations (JAK2 V617F/exon 12, CAL-R and MPL), and the absence of rearrangements in genes encoding platelet derived growth factor receptors alpha and beta (*PDGFRA/B*) and fibroblast growth factor receptor 1 (*FGFR1*). The correct diagnosis is essential to optimizing patient outcomes but remains challenging in most cases.

Here we report a case of a 78-year-old woman with a negative past medical history, who came to our Emergency Room (ER) cause of increased white blood cell (WBC) that were detected during routine checks. She was asymptomatic except for mild fatigue. Physical examination revealed pallor and mild splenomegaly. Laboratory examinations showed hyperleukocytosis with WBC count was 74.410/μL, with ANC 52,830/μL, lymphocytes 5950/μL, eosinophils 740/μL, monocytes 1490/μL, blasts 1%, promyelocytes 2%, myelocytes and metamyelocytes 14%, thrombocytopenia (P) 24.000/ μL and anemia (Hb 6,3 g/dl). The last available exams were of couple of months apart and showed a mild leukopenia and thrombocytopenia. It was taken an abdominal ultrasound scan, which showed splenomegaly (15.5 cm) and chest X-ray which was negative for pneumonia and pleural effusion. Moreover, the most frequent causes of neutrophilia were excluded. A preliminary diagnostic hypothesis of blast phase MPN was considered, and it was management with Hydroxycarbamide 1 g/die associated to support therapy. The evolution was marked by the fall of the white blood cells. The patient underwent bone marrow (BM) examinations: (i) *BM ago*

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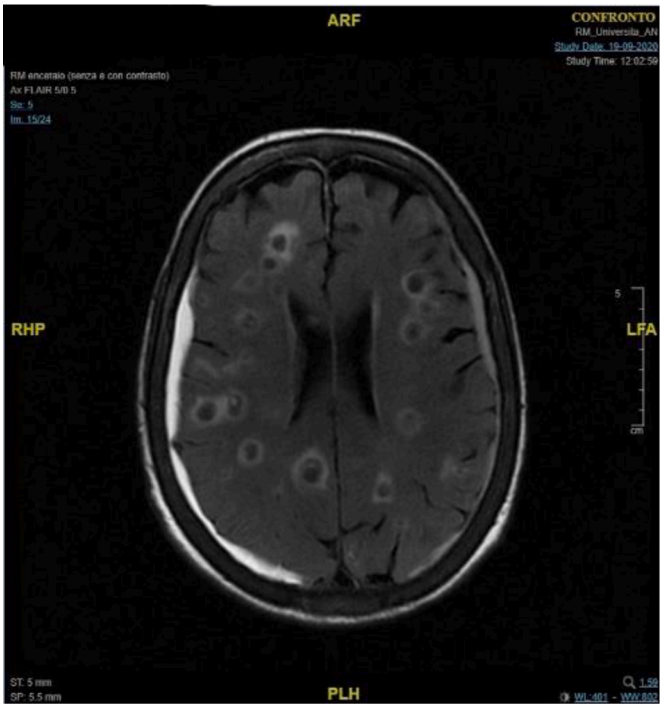

Fig. 1. Brain RMN shows multiple cortico-subcortical lesions in the brain parenchyma, cerebellum, encephalic trunk with a maximum diameter of 11,6 mm with spontaneous hyperintensity and perifocal edema.

aspirate showed hypercellular bone marrow with an elevated leucocyte/erythrocyte ratio with a reduced maturation of the myeloid lineage without blast excess (< 5%) and a reduced and dysplastic erythroid lineage. The megakaryocytes were normal and not suggestive of a Primary Myelofibrosis; (ii) *cytogenetic analysis* revealed a normal karyotype (46, XY); (iii) *flow cytometry analysis* revealed granulated and dysplastic leukocytes with the following phenotype: CD13+ CD16- CD66b- CD4+ CD33+ CD15+ MPO+ HLADR+ CD34- CD16+ CD56- TdT-, mature cells were absent (<1%). The CD34+ cells were nearly 3,3; (iv) *BM biopsy* showed hypercellular lacuna with emphasized granulopoiesis with most of the cells being MPO+ CDO15+ CD14- CD68+ and circa 4% of immature precursors CD34+/CD117-; (v) *molecular investigations* were negative for *JAK2* V617F and BCR-ABL fusion proteins. Furthermore, a sample of peripheral blood was sent to NGS evaluation that showed *CSF3R* mutation type c.1853C>T with VAF 43.9%, *IDH2* missense mutation c419G>*A* with VAF 43.4% and *STAG2* c.3097C>T with VAF 44,7%.

Three days later, mental confusion, retrograde and anterograde amnesia and space-time disorientation abruptly appeared, while blood exams didnt show any variation. The patient underwent a cranial CT scan that showed multiple cortico-subcortical lesions in the brain parenchyma, cerebellum, encephalic trunk with a maximum diameter of 11,6 mm with spontaneous hyperintensity and perifocal edema; these lesions were further confirmed with a cranial MRN (Fig. 1). Based on the symptoms and the non-specific MRN findings, the patient underwent a liquor analysis and major causes of encephalo-meningitis have been excluded.

Suddenly, the clinical presentation has worsened until the patient was on a comatose state, febrile unresponsive to paracetamol, steroid therapy and high spectrum antibiotics, requiring non-invasive mechanical ventilation. Blood tests revealed an increased leukocytosis with WBC 97,960/μL and elevated lactate dehydrogenase level (LDH 2080 U/l). After a few hours the WBC went on doubling reaching the value of 195.740μL and, later in that morning, the patient died.

A postmortem examination determined as cause of death the presence of leukemic and hemorrhagic infiltration in multiple organs, especially in spleen and lymph nodes, heart, kidneys, lungs with multiple vascular microthrombi and bronchopneumonia with hemorrhagic infiltrations, liver with portal and sinusoidal thrombi associated to parenchymal necrosis, and brain with multiple hemorrhagic lesions (Fig. 2) . BM histology showed a cellularity of nearly 100% represented by myeloid elements with a slowdown maturation, with the following characteristics on immunohistochemical positivity for myeloperoxidases, CD33 and CD15, CD34 5%, negativity for CD10, TdT, CD13, CD14, CD138, CD68, CD20, CD3, CD56.

2. Discussion

According to 2022 World Health Organization (WHO) [1] diagnostic criteria this case can be reported as a MDS/MPN with neutrophilia, a clonal hematopoietic disorder characterized by both proliferative and dysplastic features. MDS/MPN with neutrophilia is classified as an MDS/MPN overlap syndrome that is difficult distinguish from other subtypes of myeloid diseases like CML, CMML, and particularly CNL. MDS/MPN with neutrophilia is characterized by leukocytosis with dysplastic neutrophilia and an increase of their precursors (>10%), hypercellular BM with granulocytic dysplasia and blasts <20%. Karyotypic abnormalities are reported in as many as 80% of cases [2].

Recent data indicate that SETBP1 and ETNK1 mutations are relatively common in MDS/MPN with neutrophilia [3], whereas CSF3R

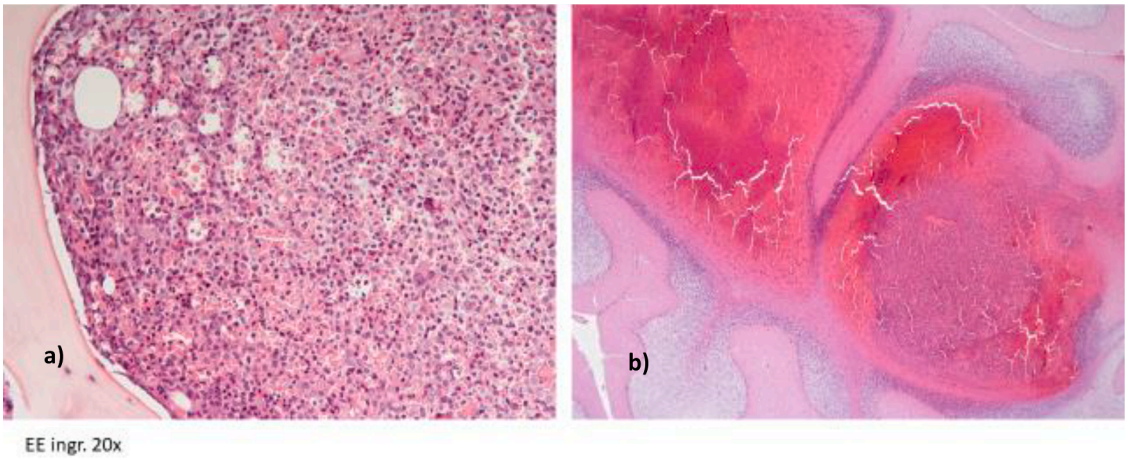

Fig. 2. a) BM biopsy shows a hypercellular BM represented mostly by myeloid elements with a slowdown maturation. b)brain parenchyma that shows hemorrhagic focal in the brain parenchyma with intravascular and intraparenchimal leukemic infiltration.

mutation is present in <10% of cases [3]. This mutation is found in a considerably larger proportion of CNL cases [4], but it does not rule out the diagnosis of MDS/MPN with neutrophilia [3]. CSF3R is the receptor for colony-stimulating factor 3 and is thought to play a prominent role in the growth and differentiation of granulocytes, structural and functional alterations of this receptor are thought to perturb the capacity of CSF3R to regulate granulocyte differentiation and to increase granulocytic proliferative capacity.

The MDS/MPN with neutrophilia remains a diagnosis of exclusion. This case report emphasis that even though aCML is a rare disease, we should promptly diagnose it for its fatal and unexpected course and the urge to initiate treatment immediately, because most of the patients die of BM failure or in blast phase. There is no specific/targeted therapy approved, even though there are a lot of clinical trials including MDS/MPN with neutrophilia like AZA+VEN+Pevonedestat, TAS1553, AZA+RUXO, CPI-0610 [5]. More studies are needed to properly diagnose and treat MDS/MPN with neutrophilia.

Informed consent

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and was approved by "Azienda Ospedaliera Universitaria delle Marche" Ethics Committee. Patient provided written informed consent.

Declarations of Competing Interest

None

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