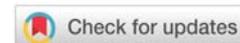




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Clinical Image

Smoldering myeloma in a patient with B12 deficiency: The importance of appropriate differential diagnosis of peripheral plasma cells

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A 79-year-old woman without relevant past medical history presented at Hospital Clínico UC Christus with progressive dyspnea and edema of lower extremities. Initial laboratory workup showed severe macrocytic anemia (hemoglobin, 5.7 gr/dL; MCV, 117 fL), associated with leukopenia (2800 u/L), low platelet count (104,000 x 10³u/L) and high levels of LDH (6500 UI/L). A direct visualization of blood film was performed, which evidenced macrocytosis (Figure 1A [Digital microscopy; Cellavision, x100 objective]), with ovalocytes and a few erythroblasts (Figure 1B), hypersegmented neutrophils and eosinophils (Figure 1C-D); findings suggestive of megaloblastic anemia. A secondary laboratory workup showed low levels of vitamin B12 (<100 pg/ml), normal levels of folate and high anti-intrinsic factor antibodies. Added to the above, in the blood smear the presence of mature plasma cells was observed (Figure 1E, one mature plasma cell for every 200 nucleated cells). In this scenario, and without secondary etiologies, protein electrophoresis evidenced a monoclonal peak of 2,7 grams (Figure 1F); immunofixation in serum evidenced monoclonal IgG lambda; and the ratio lambda/kappa was 69,2. Total body CT was performed without evidence of lytic lesions, calcium and renal function were normal. A bone marrow aspirate was performed, with the presence of 10% of plasma cells, and flow cytometry evidenced 7,2% of plasma cells (Figure 2 in red color [BD FACSCanto II]), 97% characterized as clonal plasma cells, and erythroblasts had an augmented FSC/SSC pattern (Figure

2F), suggestive of megaloblastic changes. After treatment with B12, the anemia resolved. The final diagnosis was pernicious anemia and smoldering myeloma with high risk of progression.

Plasma cells maturation initiates in lymph-nodes, and migrate quickly to the bone marrow. It is estimated through

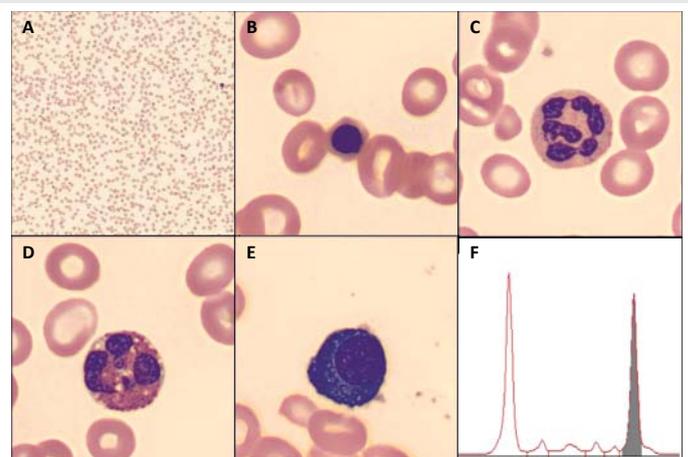


Figure 1: Peripheral blood film; digital microscopy, Cellavision. Figure A Blood smear with marked macrocytosis. Figure B An erythroblast and abundant ovalocytes. Figure C Hypersegmented neutrophil. Figure D Hypersegmented and vacuolated eosinophil. Figure E Mature plasma cell. Figure F Monoclonal peak in serum protein electrophoresis.

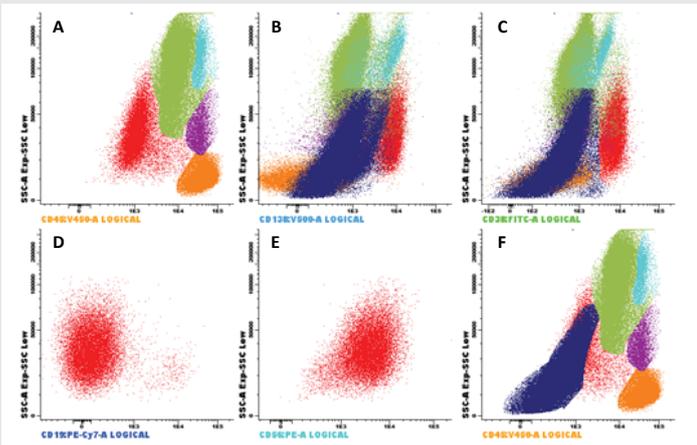


Figure 2: Bone marrow Flow Cytometry; BD FACS Canto II. In red, clonal plasma cells. In blue, erythroblast. In orange, lymphocytes. In green, neutrophils. In purple, monocytes. In turquoise, eosinophils.

flow cytometry that the median number of plasma cells in peripheral blood in patients over 60 years is 1–2 cells per uL [1]. But, when analyzing the direct visualization of the blood film, it is very infrequent to find plasma cells [2]. This implies that we must be thorough in looking for the etiology once we find them, and therefore it is important to make an adequate differential diagnosis. There are two main groups of etiologies for plasma cells in peripheral blood: reactive phenomenon or clonal disorder. Reactive processes are explained in response to IL-6 secretion, and there are a few reports with infections (SARS-COV-2 [3], Staphylococcal and E coli sepsis [4,5]), Castleman disease and [6] and Angioimmunoblastic T-cell Lymphoma [7–9], the entity with more reports in the literature. It's important to note that Epstein Barr virus and HIV are causes of reactive bone marrow plasmacytosis [10,11], but not in peripheral blood. Regarding clonal disorders, multiple myeloma is the principal diagnosis. When reactive causes are dismissed, it's preemptory to investigate the presence of a monoclonal gammopathy. The presence of clonal plasma cell in cytology is a very important marker in monoclonal gammopathy: it is quickly oriented to myeloma as the cause, because the prevalence of circulating plasma cell in MGUS is very infrequent (0% versus 17% in myeloma) [12]; and it is associated with a very aggressive disease [13], it has even been proposed to reconsider the cut points of plasma cell leukemia.

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