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Opinion

Fundoscopic Manifestations in Philadelphia-Negative Myeloproliferative Neoplasms: What to Expect Especially in Primary Myelofibrosis?

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Opinion

Philadelphia-negative (Ph-negative) myeloproliferative neoplasms (MPNs) are a heterogeneous group of hematopoietic stem cell diseases. There are clonal diseases acquired from hematopoietic stem cells and include: essential thrombocytosis (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)[1,2], target disease of this article. As they are systemic hematological diseases, they have the potential to affect multiple and different tissues and also organs, and their main complications are: thrombosis, hemorrhage and leukemic transformation. The fact is that only a few complications help in the diagnostic suspicion of the large group of these diseases, however, other signs and symptoms are often misdiagnosed or neglected as a sign of MPNs disease [1]. PMF is a hematological disorder with atypical megakaryocyte proliferation, increased cellularity, granulopoiesis and left shift, reduced erythropoiesis and/or reticulin, in addition to collagen fibrosis and extracellular hematopoiesis [3]. The classic PMF featured anemia, variable changes in platelet and leukocyte counts, bone marrow fibrosis, and splenomegaly. It is important to emphasize that the main causes of morbidity and mortality are due to the fact that patients are prone to both thrombotic and hemorrhagic events [1], however, many other signs and symptoms, with different manifestations can also be observed, such as the ophthalmologic one. The thrombotic and hemorrhagic events are usually secondary to the pathognomonic hematological disorders of MPNs and most of them can be misdiagnosed as other eye disorders [2].

Ophthalmic manifestations are extremely rare, there are few documented cases and mainly involve retinal hemorrhages (RH) at different sites [4]. Thromboembolic events in MPNs are well described, but not so well understood [3]. Blood abnormalities may be associated with different types of RH[5] and result from inefficient blood cell production or irregularities. Ophthalmological manifestations, even if rarely observed, can present as intraretinal hemorrhages and exudative detachments, venous occlusion marked with neovascularization, infiltration causing ciliochoroidal effusion, angle-closure glaucoma (GAF), bilateral papilledema and vitreous hemorrhage [6,7]. Documented extraocular manifestations of PMF include orbital and lacrimal gland involvement, ptosis secondary to tarsitis, eyelid thickening, conjunctival involvement, in addition to neoplastic infiltration with acute and bilateral GAF presentation, choroidal effusion, serous retinal detachment, and scleritis [7]. PFM shares similarities between myeloproliferative neoplasms (MPN) and its early distinction is crucial, as it can influence diagnostic strategies, therapeutic results, complications and prognosis [3]. MPNs are rare diseases, with an incidence ranging from 0.1 to 2.8/100,000 patients per year in Europe and about 0.44/100,000 patients per year in the US, data obtained from a recent report by Surveillance, epidemiology. Of these diseases, PV is the most prevalent, while MF is the least frequent, with an estimated incidence of 1.5 per 100,000 person-years and a mean age of 67 years. MPNs are diseases that mainly affect adults, with an average age of onset in the sixth decade of life, however, 20% of patients may be younger [8,9].

The current diagnosis is based on the 2016 criteria involving clinical and laboratory evaluation [1] and patients affected by MF have the worst outcome, with a median overall survival ranging from 6 to 9 years. As in the case of the two patients who had a dismal outcome due to a late diagnosis. However, the outcomes of patients with MF are improving in recent years [10], thanks to early diagnosis. Thromboembolic events in PFM result from the

involvement of large and small vessels, whether arterial or venous. Individuals with PFM have a higher number of cases of thrombosis or previous history, at diagnosis [3]. In the study conducted by Rubenstein et al. [5], which evaluated 67 eyes with hematological changes and showed that anemia or thrombocytopenia, when isolated, most likely do not cause RH, however, when both are present, it occurs in 44% of cases and when severely combined, in 70%. Thus, it is concluded that RH is much more likely to be found with anemia and thrombocytopenia combined than isolated. One of the patients with PFM in the same study presented, in addition to flame- shaped hemorrhage, a single image of dense, bilateral and round macular hemorrhage (platelets between 2,000 and 20,000 per mm3) and at autopsy, numerous vitreous, intraretinal hemorrhages were evidenced and macular, Predominantly In The Outer Plexiform Layer The appearance of extramedullary hematopoiesis most commonly occurs in the spleen and liver, and may also include lymph nodes, skin, pleura, peritoneum, lung, paraspinal and epidural spaces, usually without associated ocular findings [3].

Although advanced age and a history of thrombosis are well-established risk factors for thrombosis in ET and PV, the origin of their hypercoagulable state in general remains an enigma. Contributors include blood hyper viscosity due to erythrocytosis, abnormal platelet and leukocyte activation, and acquired resistance to activated protein C. Recently, both leukocytosis and the JAK2 V617F mutation have been identified as potential risk factors. However, there is no adequate data on the prevalence and distribution in PFM.

The risk stratification of PFM, in addition to factors such as age and previously established clinical laboratory data, incorporated some types of mutations, making these genetic markers increasingly important in the diagnosis, prognosis and treatment of the disease [1].

Presentations are most often related to anemia associated with ischemic retinopathy, neovascularization, retinal hemorrhages, and cotton wool spots [11]. Direct involvement of the eyes may also occur in the form of extramedullary hematopoiesis, similar to what occurs in leukemias [7].

These cases become important, as they present RH with a conventional aspect of the so common presentations of most retinal occlusions and provide information about a complex systemic disease that can present with rare but devastating ocular manifestations, such as CRVO. The recognition of HR allows for diagnostic suspicion different from the epidemiologically common ones and the investigation of possible systemic causes. Prompt recognition of the underlying etiology can result in adequate treatment of both systemic and ophthalmological manifestations, especially when associated with diagnosis, clinical laboratory and more recent genetic stratification. The ophthalmologist can be very helpful in diagnosing these patients, as they are rarely undiagnosed until present major thrombotic events and the symptoms or ocular presentations may precede serious extraocular complications related to PMNs. Thus, in the face of a suspicious or atypical ophthalmological finding, the possibility of an underlying hematological disorder must be ruled out, which may, therefore, enable early recognition and also begin at the right time an adequate treatment of the typical diseases, reducing morbidity and mortality in these patients [2]. In a study conducted by Carraro et al. [11], the authors observed that the prevalence of retinopathy and background lesions increased with the severity of anemia or thrombocytopenia.

It is noteworthy that in addition to the importance of identification and treatment of ocular manifestations, the clinical diagnosis of PFM, as a systemic disease must be recognized early, since life expectancy in these cases can be greatly shortened. The recognition of retinal hemorrhages, both in patient one and two, associated, in the case of patient one, with CRVO, although rare, should draw the attention of the ophthalmologist to the referral of the patient in question to the specialist in internal medicine, being able to collaborate greatly with the diagnosis as early as possible, given the morbidity and mortality.

The retinal vein occlusions (RVOs), whether in the form of CRVO or its branches occlusion, is one of the main causes of vision loss in people over 40- years-old [12] and have numerous different causes. Classic vascular risk factors, especially hypertension and aging, should not be ignored, as they represent the main genetic factors, as well as rarer causes such as PFM[6] and more recently COVID-19. After medical examinations, OVRs should be treated by specialists, as they are one of the main causes of retinal vascular diseases, right after diabetic retinopathy [12]. Even though RVO is the second most common retinal vascular disorder and may present from asymptomatic and painless in the initial stages, until sudden, moderate to severe loss of vision, with global prevalence, in 2015, ranging from 0.77%, 0.64% and 0.13%, between 30-89 years of age, other causes must be investigated, except those previously associated with risk factors, such as: advanced age, hypertension, history of acute myocardial infarction, history of stroke, high levels of total cholesterol and creatinine. RVO is usually unilateral and even with contralateral involvement, it is unlikely to occur simultaneously, even if asymmetric. Another very prevalent eye disease that may present a higher risk of development in patients with PMF is Age-related macular degeneration, as demonstrated in a large Danish cohort study. Suggesting an association with MPNs diseases in part, both due to inflammatory mechanisms and due to hyperviscosity and its microvascular disorders, in addition to findings related to retinal and choroidal ischemia and neovascularization [13].

Therefore, these cases become important, as they allow the ophthalmologist to be aware of some differential diagnoses, even if rare, and which can save or prolong lives. The increase in knowledge about the pathogenesis and molecular biology of MPNs has broadened and improved their prognostic definition in recent years. The inclusion of molecular data in survival models is already well established and recommended in PMF, while in patients with

PV and TE, the evidence is still preliminary. For the latter two, monitoring of individuals is still based more on thrombotic risk than on mortality estimates. Support ocular or systemic diagnosis and treat not only morbidities, but also help to reduce preventable mortalities. Furthermore, the correct diagnosis of this disease in its pathophysiology, symptoms and presentation will help not only in the treatment and better prognosis, but also in the recognition of new treatments for other diseases. Despite the relentless search for an earlier diagnosis, the increase in available therapies and the greater experience in management, the prognosis of patients with PMF still remains the real sensitive point in the field of NMPs and, in a way, further studies should be encouraged to achieve this. favorable results with the contribution of ophthalmology [14,15].

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