Diplopia and Vision Loss Associated With Presumed Systemic Lymphohistiocytic Disease: A Case Report

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ABSTRACT: Systemic lymphohistiocytic infiltration is a rare peculiar condition that can raise the possibility of more specific entities such as autoimmune disease, drug interaction, viral or mycobacterial infection, or malignancy. A hyper-inflammatory state can ensue leading to multi-organ failure. We report the case of a 42-year-old Jordanian male with a past history of moderate Covid-19 infection presenting with binocular diplopia and acute loss of vision in the left eye. Ophthalmic evaluation revealed limitation of extraocular motility in all directions of gaze in the left eye and a visual acuity of 6/30 with a sluggish pupil. Orbital imaging revealed a 10 mm mass at the orbital apex suspicious of malignant metastasis. A positron emission tomography CT scan showed significant pleural thickening and was highly suggestive of metastatic mesothelioma seeding to the orbit, liver, and bone. A CT guided biopsy of the right lung was negative for malignancy but had features of lymphohistiocytic pleuritis. The patient dramatically succumbed to respiratory and renal failure. Systemic lymphohistiocytic infiltration is an aggressive benign inflammatory process that may masquerade as malignancy and raise the possibility of past viral infections, autoimmune diseases, or cancer. A high index of suspicion and a multidisciplinary approach is warranted. In this particular devastating instance, a diagnostic dilemma presented to the eye clinic with diplopia, loss of vision, and an orbital mass, culminating in rapid onset respiratory and renal failure and death.

KEYWORDS: Lymphohistiocytic pleuritis, diplopia, vision loss, case report

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Background

Lymphohistiocytic infiltration is a non-specific histopathological finding that can be observed in association with other disease processes, including but not limited to, autoimmune diseases, drug reactions, infections (viral or mycobacterial), familial causes, and adjacent to or within a neoplastic process.[1-3] Some of these scenarios can lead to a hyperinflammatory state where the patient can rapidly deteriorate into multi-organ failure.[4-6] The primary disease in children is more common and familial causes have been reported to involve distant organs.[7] A search through Pub Med and Scopus revealed very limited reports of orbital and/or ocular involvement in association with benign lymphohistiocytic inflammation.[8] We report a case of a presumed systemic lymphohistiocytic infiltration presenting with diplopia and acute loss of vision in an otherwise healthy 42 year-old patient.

Case Presentation

A 42-year-old male presented to the ophthalmology clinic complaining of binocular diplopia and blurring of vision in the left eye for 5 days duration. Per his pulmonologist, he developed moderate Covid-19 (defined as evidence of lower respiratory disease during clinical assessment or imaging, with SpO_2 $\geqslant$94% on room air) 4 months prior to this presentation, with fever for 5 days and shortness of breath, but was not hospitalized and recovered without apparent sequelae. However, 90 days after his recovery, he started complaining of progressive shortness of breath. Computerized tomography (CT) scan of the chest revealed right lung loss of volume with thick nodular pleural thickening. Thereafter, video-assisted thoracoscopic surgery was performed to acquire a pleural biopsy. The histopathologic examination was reported as benign inflammation with no evidence of malignancy. Nine days after obtaining his pleural biopsy, he reported to our eye clinic complaining of gradual loss of vision in the left eye and binocular diplopia. On clinical examination, the patient had a left eye unaided visual acuity of 6/30 that did not improve with refraction, a mid-dilated pupil with a +2 reverse relative afferent pupillary defect, and scored 8/13 on the Ishihara test, along with extraocular motility limitation in all directions of gaze with binocular double vision. Slit lamp examination of the left eye was normal except for a slightly pale optic disc. The right eye had a visual acuity of 6/6 and a normal ophthalmic exam including color vision testing. His vital signs were also within normal limits. A Magnetic Resonance Imaging (MRI) of the orbit revealed a non-enhancing small soft tissue lesion within the apex of the left orbit compressing the optic nerve with surrounding edema of the extraocular muscles.

Consequently, the patient was admitted for further work up. Laboratory tests showed an increase in white blood cells (25.03×10^9/L) that were predominately neutrophils (82.9%), while his lymphocyte percentage was depressed (8%). His

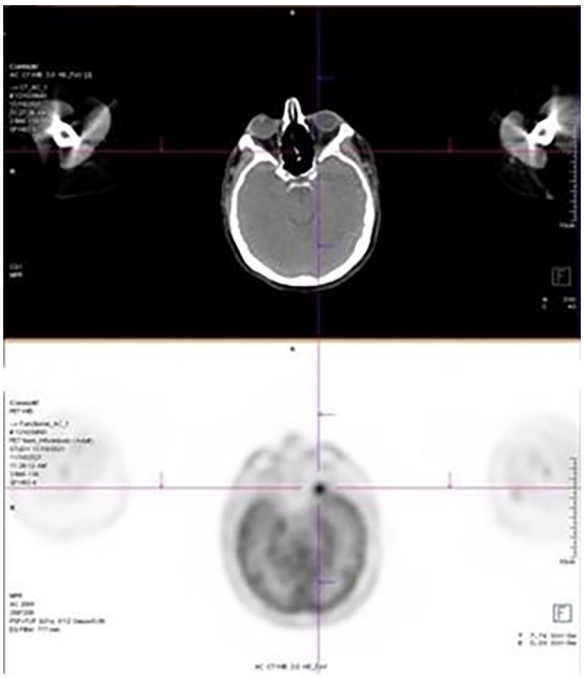

Figure 1. A Positron Emission Tomography (PET) scan showing focal intense hypermetabolic activity in the apex of the left eye with a size of 1 cm in diameter and 7.7 Standard Uptake Value. The findings were highly suspicious of metastatic disease.

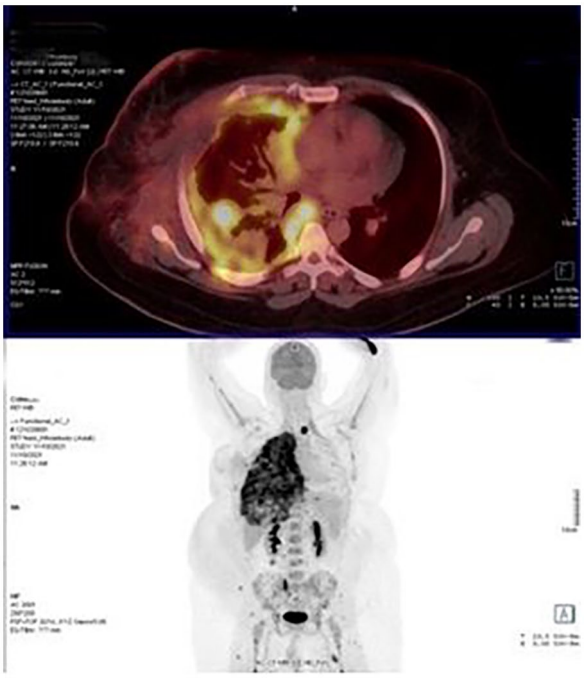

Figure 2. A Positron Emission Tomography (PET) scan showing nodular thickening of the right pleura with intense hypermetabolic activity and underlying infiltrative nodular lung changes and loss of volume. The features were highly suspicious for mesothelioma.

hemoglobin level was slightly below normal (11.9 g/dL) while his platelet count was within normal limits (239 000 per μL of blood). The Erythrocyte Sedimentation Rate (ESR) was increased (80 mm/h) as well as the C-Reactive Protein (CRP) (139.8 mg/L). The oncology team was consulted on the case but found no hepato- or splenomegaly on physical examination and subsequently recommended a Positron Emission Tomography (PET) CT scan to rule out metastatic disease. The scan showed a focal intense hypermetabolic activity in the apex of the left orbit (at the site of the diagnosed soft tissue lesion by MRI) with a Standardized Uptake Value (SUV) of 7.7 and a size of 1 cm in diameter, highly suggestive of malignancy (Figure 1). The scan also disclosed a 2.5 cm nodular thickening of the right pleura with intense hypermetabolic activity and underlying infiltrative nodular lung changes and loss of volume with a prominent hypermetabolic collapsed tissue/round-like mass lesion within the superior right lower lobe (Figure 2). Two small hypermetabolic left liver lobe lesions and a small hypermetabolic nodule within the left adrenal gland were also noted and deemed likely metastatic. Hypermetabolic activity in the left thyroid gland, bone marrow, and upper thigh muscles warranted further investigation.

The patient subsequently underwent a CT-guided biopsy of the right lung. Histopathological examination showed a benign lymphohistiocytic inflammatory process involving the pleural tissue with no pathological evidence of malignancy or specific infections after the utilization of multiple special stains including CD1a and S100. The inflammatory infiltrate was composed of histiocytes, lymphocytes, rare plasma cells with scattered multinucleated giant cells that percolate the adjacent skeletal muscles, and adipose tissue (Figure 3).

The patient's respiratory functions deteriorated rapidly as he developed mixed respiratory and metabolic acidosis. The patient was put on broad spectrum antibiotics and received oxygen by nasal cannula. He succumbed into multi-organ failure and chest imaging revealed worsening right sided infiltration. The patient remained hypotensive, febrile, and tachycardic despite all resuscitative interventions to improve his oxygenation and blood pressure until he passed away 3 weeks after his initial presentation.

Discussion

This case represents a diagnostic dilemma as well as an unusual presentation of a possible hyper-inflammatory state. Orbital involvement of a systemic lymphohistiocytic disease provides a new perspective on orbital masses as well as autoimmune diseases. Lymphohistiocytic pleuritis, which was the most challenging aspect of our patient's condition, can be multifactorial. It might be caused by infectious agents such as mycobacterial and fungal infection and bacillary angiomatosis.[9,10] These were excluded in our patient by performing special stains on our biopsy (Ziehl-Neelsen, GMS, Steiner-Steiner). Drug reactions were also excluded as our patient did not take any regular medications, nor did he receive any kind of antiviral treatment during his Covid-19 episode. Autoimmune etiologies remain in the differential diagnoses for this case despite the ambiguity of clinical and laboratory assessments, as the basic autoimmune

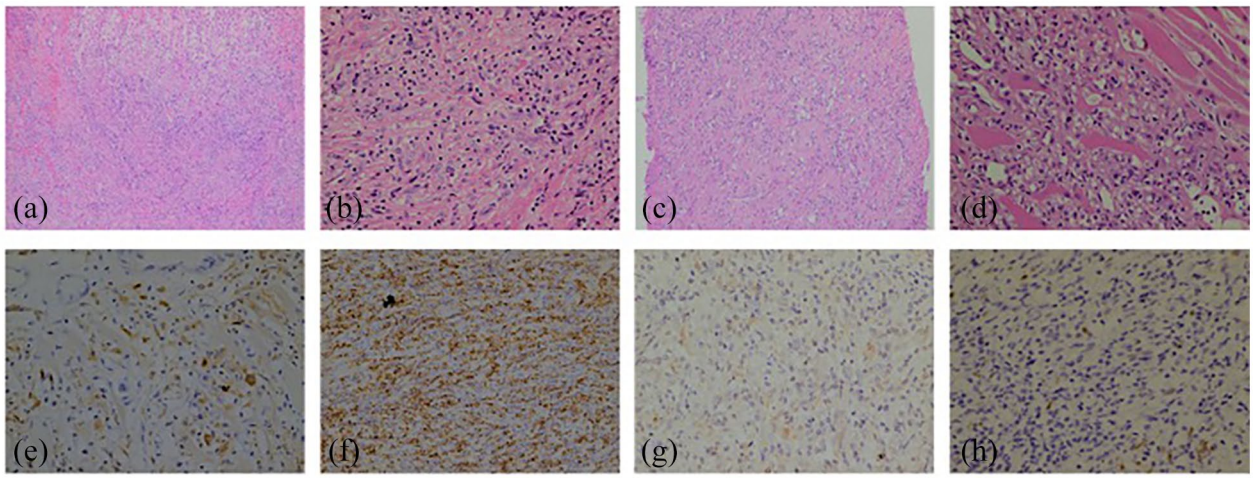

Figure 3. Lymphohistiocytic pleuritis. (A) Dense inflammatory reaction admixed with fibroblastic proliferation, H&E, low power view (10×). (B) Prominent lymphohistiocytic infiltrate with fibroblastic proliferation and collagen deposition, H&E, high power view (40×). (C) Pleural core biopsy. (D) Lymphohistiocytic reaction infiltrating the adjacent skeletal muscles, H&E, high power view (40×). (E) Positive expression of cytokeratin immunohistochemical stain, pleural core biopsy. (F) Positive expression of CD68 immunohistochemical stain. (G) Negative expression of calretinin immunohistochemical stain. (H) Negative expression of WT-1 immunohistochemical stain.

work up was negative. IgG4-related disease was in the differential diagnosis of this case, but his IgG levels were within normal limits. Unfortunately, an autopsy was not performed to shed more light, if any, on any other possible unknown pathology in multiple organs.

Covid-19-associated cytokine storm has been linked to lymphohystiocytosis.[11,12] However, the extended period between Covid-19 recovery and the onset of breathlessness makes such an explanation less likely. On the other hand, Covid-19 vaccines have also been reported to cause similar histopathological findings.[13] These changes, however, usually cause cutaneous manifestations in vaccinated individuals. In any case, our patient was never vaccinated against Covid-19. Given the multiplicity of lesions in this case, the timing of presentation and the similar imaging signal intensities, the orbital lesion may be a part of this widespread lymphohistiocytic process.

Conclusion

Systemic lymphohistiocytic infiltration is a masquerader that can be observed with many pathologies, including autoimmune diseases, drug reactions, post-viral infections, or familial causes. A high index of suspicion and a multidisciplinary approach is warranted in such cases. In this particular devastating instance, a diagnostic dilemma presented to the eye clinic with diplopia, loss of vision, and an orbital mass, culminating in rapid onset respiratory and renal failure and death.

Author Contributions

NA was responsible for conception and supervision, data proofing and writing the final manuscript. AO wrote the initial two drafts and was responsible for obtaining data images and incorporating laboratory data into the manuscript. MA and TA read the pathology slides and were responsible for histopathology image production and commentary. M. Al-Abbadi re-checked the pathology slides, wrote the third draft and approved the final images. All authors approved the final manuscript and agreed to be equally accountable for this work.

Ethics Approval and Informed Consent

Ethical approval was waived by the Institutional Review Board at Jordan University Hospital as this is a case report with no risk of harm to the patient. Written informed consent was obtained from patient's next of kin to report the case.

Availability of Data and Materials

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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