American Journal of Ophthalmology Case Reports 33 (2024) 101996

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Susac syndrome in a patient with chronic myelocytic leukemia: Consequence or coincidence?

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ARTICLE INFO

Keywords:
Arterioarterial
Arteriovenous
Autoimmune disorder
Brao
Chronic myelocytic leukemia
Nonperfusion area
Microaneurysm
Susac syndrome

ABSTRACT

Purpose: In this study, we report a patient who presented with both chronic myelocytic leukemia (CML) and Susac syndrome (SS).

Observations: A 45-year-old male diagnosed with CML in the blast phase sought consultation due to a deterioration in vision in his right eye. He also had hearing loss and severe migraneous headaches. Best corrected visual acuity was light perception and 20/20 in the right and left eyes, respectively. The slit lamp examination and intraocular pressure were within normal ranges for both eyes. Upon dilated fundoscopy, organized vitreous hemorrhage was observed in the right eye, while the left eye exhibited extensive sclerotic vessels with retinal neovascularization in the periphery. Ultrasound of the right eye showed tractional retinal detachment. Optical coherence tomography of the left retina showed thinning of the retina in temporal macula. Fluorescein angiography revealed a substantial nonperfused region in the peripheral left retina, accompanied by arterioarterial and arteriovenous collaterals, along with microaneurysms. MRI showed scattered foci of hyperintensity within the supratentorial white matter, mostly subcortical on T2-weighted and fluid-attenuated inversion-recovery. The patient received a diagnosis of SS and was subsequently referred to the neurology service for further assessment and potential treatment.

Conclusion and importance: SS may manifest as a presentation of CML. It is advisable to conduct investigations for SS in CML patients experiencing neurological, ophthalmological, or otological symptoms.

1. Introduction

Susac syndrome (SS) is an infrequent condition believed to be caused by the immune system, leading to the blockage of small-to-medium-sized blood vessels within the brain, retina, and inner ear. This syndrome is characterized by a triad of encephalopathy, visual disruptions, and sensorineural hearing impairment and other vestibulocochlear symptoms. The complete triad is present in only 13 % of patients at disease onset.[1,2]

Chronic myeloid leukemia (CML) is a rare myeloproliferative neoplasm (MPN). A correlation between the autoimmune disorders and hematological malignancies has been reported.[3,4]

In this study, we present a unique case where SS was observed in a patient experiencing the accelerated phase of chronic myeloid leukemia (CML). Following a thorough literature review on September 20, 2023, utilizing PubMed, Google Scholar, and the Google search engine with the keyword "Susac" and "chronic myelocytic leukemia", no prior reports were identified regarding the co-occurrence of Susac Syndrome and chronic myelocytic leukemia.

2. Case report

A 45-year-old male diagnosed with CML in the blast phase sought consultation due to a deteriorating vision in his right eye. The patient reported experiencing blurring in his right eye three months prior to his appointment, which subsequently progressed to a complete loss of vision after two months. No other associated ocular symptoms were present around the same time. During a similar timeframe, he lost his hearing completely in both ears. A month prior to his visit with us, he developed severe migraneous headaches. He had received a diagnosis of the chronic phase of chronic myeloid leukemia (CML) fourteen months prior to this consultation. He had been receiving dasatinib on an intermittent

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https://doi.org/10.1016/j.ajoc.2024.101996
Received 29 September 2023; Received in revised form 22 December 2023; Accepted 12 January 2024
Available online 23 January 2024

basis since his CML. His most recent dose of dasitinib had been administered five months before his visit to our clinic. Best corrected visual acuity was light perception and 20/20 in the right and left eyes, respectively. The slit lamp examination and intraocular pressure were within normal ranges for both eyes. Neovascularization of iris and angle were not observed in either eye. Upon dilated fundoscopy, an organized vitreous hemorrhage was observed in the right eye, while the left eye exhibited extensive sclerotic vessels with retinal neovascularization in the periphery (Fig. 1a and b). The comprehensive investigation into potential infectious and noninfectious causes of occlusive retinal vasculitis, encompassing assessments for tuberculosis, Lyme disease, syphilis, sarcoidosis, herpes family viruses (HSV1, HSV2, VZV, EBV), antinuclear antibody (ANA), antineutrophilic cytoplasmic antibody (ANCA), HLA-B12, HLA-B5, HLA-B44, C3, C4, and CH50, yielded negative results or fell within the normal range. Optical coherence tomography (OCT) of the left retina showed thinning of the retina in temporal macula (Fig. 1c). Fluorescein angiography (FA) revealed a substantial nonperfused region in the peripheral left retina, accompanied by arterioarterial and arteriovenous collaterals, along with microaneurysms (Fig. 1d and e). Fig. 2 demonstrates the ultrasound of the right eye with extensive tractional retinal detachment and vitreous hemorrhage. Magnetic resonance imaging (MRI) showed scattered foci of hyperintensity within the supratentorial white matter, mostly subcortical on T2-weighted fluid-attenuated inversion-recovery (FLAIR) images (Fig. 3). No abnormalities were reported in the auditory system and cranial nerve eight on the MRI imaging. The patient received a diagnosis of SS and was subsequently referred to the neurology service for further assessment and potential treatment. Additionally, due to the significant nonperfused area detected in the left retina, retinal photocoagulation of the nonperfused region was carried out. He is a candidate for pars plana vitrectomy of the right eye once his systemic condition becomes stable.

3. Discussion

By definition, syndrome is a cluster of symptoms that consistently co-occur or a condition distinguished by a set of interconnected symptoms. SS is typically divided into two clinical subtypes: one marked by significant neurological symptoms and the other by ophthalmological issues, including recurrent episodes of BRAO (branch retinal artery occlusion), often accompanied by less severe or even no neurological manifestations. Neurological symptoms are varied and include cranial nerve disorders, seizure and dementia[1,2]; however, headache, while not specific, represents the most common symptom, impacting as many as 80% of patients. This headache may manifest with characteristics resembling migraine symptoms. BRAO is the classical retinal finding in

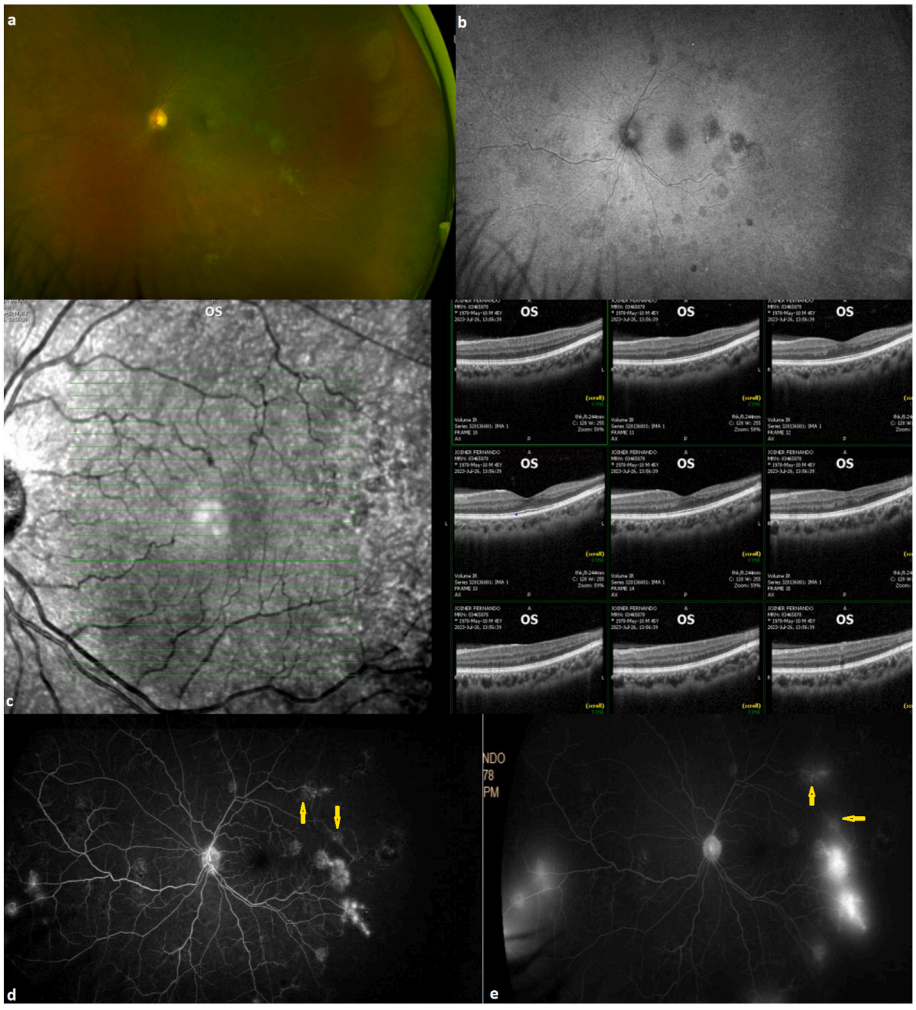

Fig. 1. (a,b) Wide-field multicolor fundus photo and blue autofluorescence of the left eye respectively showing sclerotic vessels with retinal neovascularization in the periphery of left retina. (c) Optical coherence tomography (OCT) of the left retina revealed temporal macular thinning. (d,e) The mid and late phase of fluorescein angiography (FA) of the left eye, a significant nonperfused area was observed in the peripheral left retina, along with the presence of arterioarterial and arteriovenous collaterals, as well as microaneurysms (yellow arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

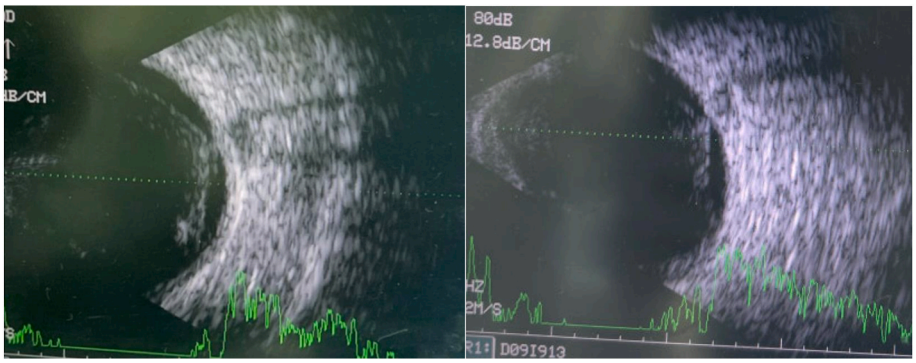

Fig. 2. Ultrasound of the right eye demonstrating extensive tractional retinal detachment with vitreous and subretinal hemorrhage.

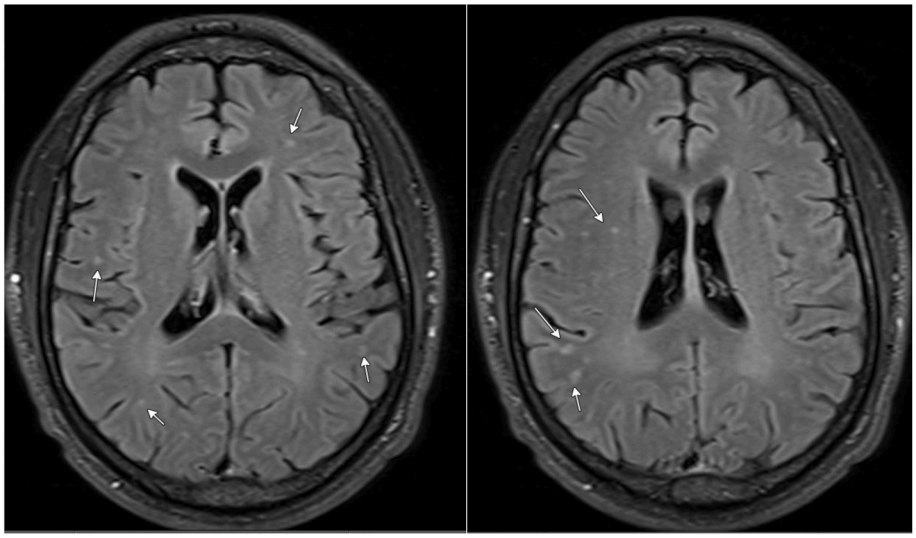

Fig. 3. Axial T2 fluid-attenuated inversion-recovery (FLAIR) imaging of the brain. There are multiple hyperintense white matter lesions particularly in the subcortical white matter (white arrows).

SS. Retinal involvement can be asymptomatic when BRAO affects small arterioles in the periphery. These patients can present with retinal neovascularization and vitreous hemorrhage.[5–7]

The diagnosis of SS relies on the clinical symptoms and results obtained from retinal FA, brain MRI, and audiometry. The snowball lesions detected in the corpus callosum on MRI are highly indicative and characteristic, indicating the presence of multiple small infarcts in the callosal tissue. Over time, these lesions may progress and transform into "punched out" callosal defects. Another common MRI finding in SS patients is small hyperintense lesions predominantly involving the corpus callosum, white matter, cerebral cortex, and deep gray structures on T2-weighted images, diffusion-weighted imaging (DWI), and FLAIR.[8] Arterial wall hyperfluorescence (AWH) can be regarded as a definitive sign of retinal involvement in active SS.[7] Another significant finding on FA in SS is the presence of capillary nonperfusion (CNP) and retinal microaneurysms without any detectable leakage[1]; however, characteristic signs of retinal branch ischemia in fundoscopy or spectral domain OCT can be the presenting signs of ocular involvement in SS. Additionally, arterioarterial and, less frequently, arteriovenous collaterals with microaneurysms have been described as novel ophthalmological observations in SS. These collateral vessels are situated distant from the optic disc and typically develop at a later stage in the disease progression.[6,7]

CML is a relatively uncommon type of MPN, with an occurrence rate ranging from 0.7 to 1.0 per 100,000 individuals.[9] Autoimmune disorders have been observed in chronic MPNs including CML.[4] Recent research has demonstrated T-regulatory cells exhibit dysfunction in MPNs, leading to an inadequate regulation of autoreactive cells and abnormal production of autoantibodies such as antinuclear antibodies, rheumatoid factor, and antiphospholipid autoantibodies.[10] Additionally, immune thrombocytopenic purpura, Crohn's disease, polymyalgia rheumatica, and giant cell arteritis have been reported in MPNs.[11,12]

In a retrospective study conducted by Galimberti et al.[4] on medically evident MPN patients, 8% of patients had autoimmune diseases (AD).[4] Longley et al.[13] reported biopsy proven skin vasculitis in six patients. They also noticed three cases with visceral vasculitis.

In certain situations, the connection between hematological neoplasms and autoimmune disorders has also been attributed to the therapies employed for the treatment of hematological malignancies, such as interferon, fludarabine, busulfan, tyrosine kinase inhibitors, and, more recently, immunotherapy[4]; however, since the diagnosis of CML, the patient was on dacitinib and autoimmune diseases (ADs) have not been reported in patients on dacitinib therapy.[14] It is important to note that dacitinib belongs to a category of drugs known as kinase inhibitors, functioning by impeding the activity of an anomalous protein that triggers the proliferation of cancer cells, thereby impeding the dissemination of cancerous cells.[15]

Our patient had severe migraneous headaches and T2-weighted and FLAIR MRI findings highly indicative of brain involvement. Additionally, ischemia in fundoscopy, thinning of the retina in spectral domain OCT, and arterioarterial and arteriovenous collaterals with microaneurysms were strongly suggestive of eye involvement. The absence of

typical signs in our patient, including snowball and/or punch out lesions in the corpus callosum on MRI and typical BRAO in retinal arterial system, can be attributed to the advanced stage and late phase of SS in our patient. Moreover, he was undergoing aggressive chemotherapy with cytotoxic medications such as idarubicin and cytarabine, which can be an efficacious treatment regimen for both SS and CML.

Our thorough literature search revealed no identified or unidentified condition other than SS for the combination of hearing loss and occlusive retinal vasculitis with arterioarterial and arteriovenous collaterals, microaneurysms, migraine-like headache, and brain MRI changes. While some of these findings may sporadically appear in Chronic myeloid Leukemia (CML), the amalgamation points to SS. It is imperative to underscore that the distinctive alterations observed in the brain MRI of our patient have not been documented in existing literature in CML patients. Consequently, we cannot categorize all of these findings in our patient as indicative of isolated CML as an entity.

The resolution of BRAO in SS depends on various factors, including the severity of the occlusion, the extent of damage to the retinal tissue, and the response to treatment. In some cases, with appropriate and timely management, there may be improvement or resolution of the BRAO. As explained earlier, treatment often involves addressing the underlying autoimmune process and may include immunosuppressive therapy. That can also explain why we did not observe a typical BRVO in our patient.

We might be criticized for not conducting a lumbar puncture and audiometry on our patient. However, it is important to note that the patient declined to undergo a lumbar puncture due to its invasive nature. Moreover, because the patient had complete deafness, and conductive hearing loss could not account for it, we opted not to conduct audiometry. Furthermore, the suboptimal quality of FA images can be attributed to our retinal imaging device settings.

Considering the chronological sequence of events and the fact that our patient was diagnosed with CML before experiencing any brain, eye, or ear involvement, we hypothesized that CML could be the underlying cause, with SS possibly being an associated effect.

Conclusion: SS may manifest as a presentation of CML. It is advisable to conduct investigations for SS in CML patients experiencing neurological, ophthalmological, or otological symptoms.

Statement of ethics

Ethics approval was not required in accordance with local guidelines and University of Florida Intuitional Review Board.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Data availability statement

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

Consent for publication

The written informed consent was obtained from the patient for publication.

CRediT authorship contribution statement

Arash Maleki: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Khushi Saigal:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Jeslin Kera:** Writing – review & editing, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors express their gratitude to Dr. Ibrahim Sacit Tuna, MD and Bryce E. Buchowicz, MD for the interpretation of the MRI images.

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