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Case Report

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More than Meets the Eye: Orbital Swelling in an Adolescent with Sickle Cell Disease

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ABSTRACT

Periorbital swelling is a clinical presentation with a broad differential and potentially deleterious consequence. Causes range from benign, including allergic reaction, to vision- and life-threatening, including orbital cellulitis and orbital infarction. The recent climate of SARS-CoV-2 has further complicated this differential, as the virus poses broad clinical presentations with new manifestations reported frequently. Rapid identification of the underlying etiology is crucial, as treatment approaches diverge greatly. Here, we report the case of an African American adolescent male with a history of homozygous sickle cell anemia presenting to an inner city hospital with bilateral periorbital swelling amid the coronavirus pandemic. Differentials, including orbital cellulitis, COVID-MIS-C, orbital inflammatory syndrome, Hoagland sign, and orbital infarction secondary to sickle cell crisis are contrasted. We contrast our case with 12 case reports of orbital infarction in the setting of sickle cell crisis within the past 10 years, highlighting how these presentations, along with commonly reported findings of orbital infarction, compare with our patient.

Keywords: Orbital edema; Sickle cell disease; Adolescent; Orbital edema etiology

INTRODUCTION

Periorbital edema is a presenting finding of a broad range of clinical diagnoses, from benign to severe. This differential is further clouded by sickle cell anemia, which predisposes to infection and inflammation. Sickle cell anemia is an autosomal recessive disease caused by a mutation at position 6 of the globin chain of beta-hemoglobin, wherein a hydrophobic valine is substituted for the hydrophilic glutamic acid[1]. Due to this substitution, conditions leading to reduced oxygen saturation of the globin chain cause the hydrophilic protein regions to juxtapose, with resultant erythrocyte sickling and cell-to-cell adhesion[2]. Both their sickled shape and intracellular adhesion contribute to slowed capillary transit times, allowing the erythrocytes' membrane adhesion molecules to more readily adhere to selectins and adhesion molecules expressed on the vascular endothelial surface[3]. Inflammation results from the resultant hemolysis and vaso-occlusion [1-6]. This pathophysiology results in early splenic infarction and subsequent immunodeficiency [2,4].

Because of these changes, a patient with a history of sickle cell anemia presenting with periorbital edema has a particularly broad differential, requiring thorough analysis of history and physical exam

findings paired with laboratory studies and diagnostic imaging. Here, we present the case of a 14-year-old male with SCD presenting with periorbital swelling in the setting of ambiguous imaging studies. We analyze differentials including periorbital cellulitis, orbital inflammatory syndrome, Hoagland's sign, COVID-MIS-C, and orbital infarction secondary to sickle cell crisis.

Case presentation

The patient was a 14-year-old African-American male with a history of homozygous sickle cell (HbSS) anemia with multiple vaso-occlusive crises, posterior reversible encephalopathy, essential hypertension, and reactive airway disease. He presented with bilateral periorbital swelling of one-day duration. He was in usual health until two days prior to admission when he developed a constant, moderate non-radiating lumbar back pain unresponsive to oxycodone and acetaminophen. The next day, he noted right eye swelling which progressed over the course of the day to involve the left eye as well. Worsening of the periorbital swelling prompted his hospital visit.

Upon admission, he denied fever, headache, vision changes, photophobia, discharge, itchiness, and pain with extraocular movements. He had no known exposure to potential allergens and no recent swimming pool use. In the past five years, while on hydroxyurea, he had five admissions for sickle cell crises with vaso-occlusive manifestations including back pain, shoulder pain, long bone pain and acute chest syndrome; one admission was complicated by seizures with evidence of posterior reversible encephalopathy syndrome on imaging. Given the severity of his complications, he was placed on prophylactic transfusion protocol – the frequency of which were limited due to the COVID-19 pandemic. He denied any history of ocular swelling associated with sickle cell crises.

In the emergency department, he was febrile (39.3 C) and tachycardic (165 bpm), but otherwise vitally stable. Physical exam noted bilateral periorbital swelling without erythema, discharge, or tenderness; sclerae were anicteric and conjunctiva were clear without exudates or hemorrhage; pupils were equally reactive, and extraocular movements were intact. The physical exam, including back exam, was otherwise unremarkable.

Admission laboratory studies showed neutrophil-predominant leukocytosis (86.5% neutrophils; 21.4 k/uL) with elevated monocytes (12%; 2.90 k/uL) as well as elevated d-dimer (1711 ng/mL), CRP (26 mg/dL), and sedimentation rate (38 mm/s); a mildly microcytic anemia (Hgb 9.5 g/dL; MCV 75.9 fL) with elevated RDW (19.4%; immature reticulocyte fraction 0.64%), lactate dehydrogenase (LDH; 1786 IU/L), and reticulocytes (5.7%) was also noted. Chemistry panel was unremarkable and troponin as well as pro-BNP were negative. Urinalysis revealed proteinuria but was otherwise unremarkable. Suspecting a potentially infectious process, blood and urine cultures were sent. Diagnostic imaging in the emergency department included an ECG showing sinus tachycardia, an echocardiogram revealing a mild pericardial effusion, and a chest x-ray showing chronically prominent markings in lung fields without acute changes. A CT of the orbits without contrast demonstrated periorbital soft tissue swelling with abnormal soft tissue density material in the lateral extraconal space without evidence of maxillary, ethmoid, sphenoid and frontal sinusitis (Figure 1). He was admitted to PICU for observation overnight given his toxic presentation; immediate management included hydration, analgesia, antibiotics, and red blood cell transfusion. He was subsequently downgraded to the pediatric floor for further management.

On the first day of admission, his symptoms progressed to include mild pain with extraocular movements and small amounts of purulent discharge from both eyes. To differentiate infective versus infarctive processes, a follow-up MRI of the orbits and facial bones with and without contrast was ordered. Imaging revealed periorbital fatty stranding (right more so than left) with extension to the bilateral extraconal spaces and apparent involvement of the lateral rectus muscles (Figure 2). Additionally, there was some subtle rim enhancement along the right optic nerve compared to the left. Ophthalmologic exam was largely unchanged from admission with newly noted right-sided entropion with associated epithelial defect of the nasal cornea. Visual acuity remained unaffected

on daily assessments, and painful extraocular movements resolved within two days.

He was followed by hematology, infectious disease, and ophthalmology for the remainder of his hospitalization and his symptoms resolved within four days. Complete blood count and inflammatory markers including c-reactive protein and d-dimer were trended throughout hospitalization (Figure 1). Blood cultures and throat cultures remained negative, though urine culture demonstrated gram positive cocci (<10 000 cfu/mL). Hospitalization was prolonged to a total of eight days due to persistent twice daily fever spikes (Figure 1). Recurrent fevers prompted further investigation into potential etiology, with vaso-occlusive crisis, orbital cellulitis, SARS-COV-2-associated multisystemic inflammatory syndrome, auto-immune, and infectious sequalae as possible differentials. Further work-up was performed and negative, including SARS-CoV-2 PCR (antibody blood testing was not yet available at the facility), heterophile-antibody testing, ANCA/ANA screening, rapid influenza antigens (Flu A and B), and thyroid function tests. He was discharged with scheduled outpatient follow-up to hematology and ophthalmology within two weeks. Follow-up appointments yielded no persistent deficits.

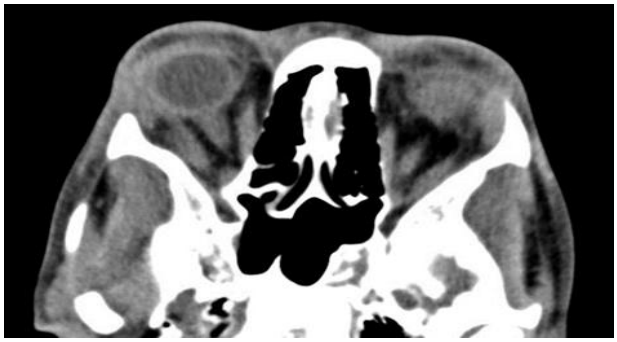

Figure 1. Orbital CT without contrast demonstrating soft tissue swelling

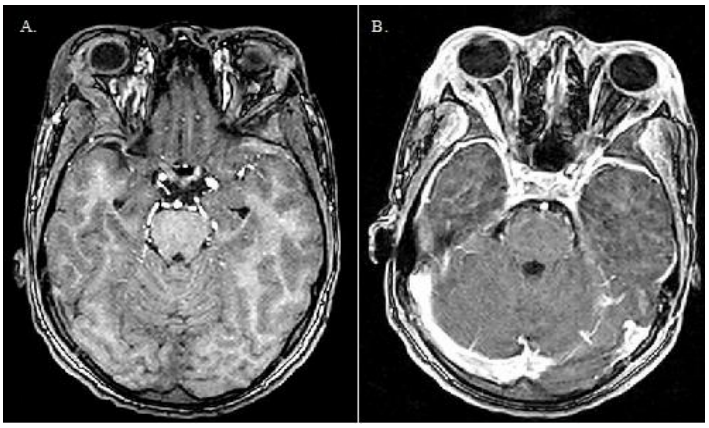

Figure 2. MRI of orbits and facial bones, T1 vibe axial images pre- (A.) and post-contrast (B.). Periorbital stranding (R>L) with extension into bilateral extraconal spaces and apparent lateral rectus involvement.

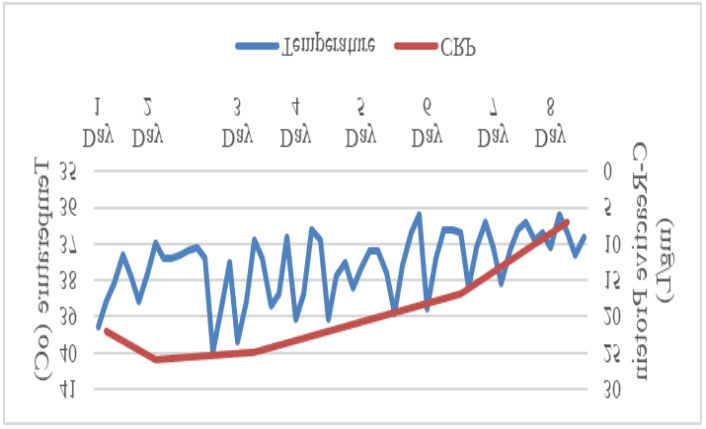

Figure 3. Trended temperature and c-reactive protein levels across hospitalization.

DISCUSSION

Narrowing the Differential

This case presented a diagnostic challenge due to the presence of multiple signs and symptoms indicative of different disease processes. Establishing the etiology was further complicated by residual, daily febrile spikes in the setting of an established antibiotic regimen. Because of the complexity of this presentation, differentials including periorbital cellulitis, orbital inflammatory syndrome, COVID-

MIS-C and Epstein-Barr virus-induced periorbital edema were explored.

Orbital infectious processes exist on a spectrum ranging in severity from preseptal cellulitis to orbital cellulitis and orbital abscess [7]. Such orbital infections are most often due to contiguous extension of rhinosinusitis (87% of cases), and less commonly, due to orbital trauma or hematogenous spread[7]. Because the etiology is often an extension of an existing infection, orbital infections are typically unilateral, presenting with symptoms ranging from isolated periorbital edema to proptosis, impaired extraocular motility, and loss of vision [7,8]. Periorbital cellulitis was an initial differential in our case due to the patient's concomitant sickle cell disease (and associated relative immunocompromised state[2]), purulent discharge, fever, and leukocytosis. Deterrents to this diagnosis included bilateral presentation as well as non-specific imaging findings without evidence of sinusitis, history of trauma, or positive blood cultures.

Orbital inflammatory syndrome (OIS) is an autoimmune-derived periocular edema with characteristically associated fever and pain with extraocular movements [9]. While classically occurring in the fourth to fifth decade, six to 15% of patients affected are children[9]. The frequent unilateral presentation seemingly negates the assumed autoimmune pathophysiology[9]; however, the condition is associated with locally elevated interleukin-1 and unique toll-like receptors in those affected, suggesting an altered innate immune response [9]. A large proportion of those affected have associated elevated serum IgG_4, suggesting a potential relationship to IgG_4-related diseases[9]. While our patient did present with elevated CRP, this was ruled out as a differential in our case for several reasons. First, initial autoimmune screen for ANCA and ANA were negative. Second, imaging demonstrated no evidence of extra-ocular muscle thickening, a typical imaging finding of OIS. Third, our patient recovered in the absence of steroid therapy, which is typically required for OIS resolution [9].

Infectious mononucleosis secondary to Epstein-Barr virus is a common pediatric disease producing a classic triad of fever, lymphadenopathy and pharyngitis [10]. Less commonly reported is transient bilateral upper lid edema called Hoagland sign [10]. This edema presents ephemerally at the disease's outset without associated inflammation, tenderness, or hindrance to extraocular movements/vision [10]. Due to the paucity of literature on this presentation, the pathophysiology remains unclear, though nasopharyngeal viral replication with associated lymphoproliferation or lymphatic obstruction is thought to be involved [10]. Hoagland's sign was considered in our patient given the rapid resolution of his periorbital swelling and the ongoing twice-daily fevers; this differential was weighted less heavily in the setting of a negative heterophile-antibody test.

Because of the local severity of the coronavirus pandemic, a multisystemic inflammatory syndrome secondary to SARS-COV-2 had to be ruled out. Nasopharyngeal swabs were sent on the first and fourth days of hospitalization, both of which were negative; while antibody testing would be optimal to rule out prior infection, this testing was not yet available at our facility. We were unable to find any case reports describing periorbital edema as a manifestation of SARS-CoV-2, though there are cases of atypical orbital cellulitis in the setting of SARS-CoV-2 coinfection [11].

Bilateral Orbital Infarction Secondary to Sickle Cell Crisis: A Closer Look

Despite this broad differential, it was noted that the periorbital edema was preceded by lumbar pain that echoed the patient's prior vaso-occlusive presentations. While bone infarction is not uncommon in sickle cell disease, orbital involvement is less commonly described. Pathophysiology involves vaso-occlusion of vasculature supplying the orbit or orbital bones, resulting in orbital bone infarction with or without associated subperiosteal hematoma[12]. This presentation occurs more commonly in male youths, with the average age of presentation being 14 years, due to increased marrow space compared to adults [13]. One review of 30 cases of orbital infarction noted a predominance for HbSS halotype, followed by sickle-beta-thalassemia, and lastly HbSC [12]; our review revealed comparable prevalence (Table 1). As such, predominant age, gender, and sickle cell haplotype

seen in orbital infarction is consistent with our patient.

Bilateral presentations are common (Table 1), typically beginning unilaterally and progress to involve the opposite eye [14]. Such presentations could be due to either direct extension of the original site of occlusion or a second area of occlusion. Notably, the two most commonly reported bones involved in bilateral presentations include the sphenoid (especially the greater wing [15]) and the frontal bone[14], both of which cross the midline, portending a contiguous extension of one process. The predominance of bilateral presentation further purported orbital infarction as a likely differential for our patient.

Infarcted bone generates a localized inflammatory response, which rapidly spreads to the orbits, producing clinical manifestations of pain and proptosis [5]. The associated tissue swelling is further complicated by hematomas, which may be intracranial (epidural) or orbital (subperiosteal). One postulated mechanism of hematoma formation is extravasion of blood from necrosed vessel walls [1,5, 16]; more likely however is that pressure of the obstructed vessels is transmitted to the periosteum with resultant bursting of bridging veins[2]. Comparable orbital subperiosteal hematomas are observed in bleeding disorders and in sudden increases in venous pressure, including delivery, vomiting, and strangulation[2]. While our patient demonstrated no evidence of hematoma on imaging, the development of pain with extraocular movements suggested an increasing edema beginning to impair ocular motility. If untreated, the combined effects of hematoma and edema-associated pressure can result in orbital compression syndrome. Syndromic manifestations include proptosis, limited ocular motility, corneal hypesthesia and optic nerve dysfunction; further compromise of the optic nerve can result in permanent blindness [5].

Prompt diagnostic imaging is suggested in all cases of suspected orbital infarction, with CT/MRI often providing images sufficient to confirm the diagnosis[1]. Initial imaging is often with CT to rule out an infective process; soft tissue swelling, fatty stranding, and fluid collections may be evident on such images [2, 5, 16-18]. Subsequent imaging includes MRI studies, with soft tissue findings including lateral wall fluid collections and edema with associated subperiosteal hematomas as well as lateral rectus muscle deviation[1,4,12-14,19]. More notably, bone findings include abnormal bone marrow signal, heterogenous enhancement of the marrow, and edema[5,18]. Absence of evidence of osteal abnormalities deterred our definitive diagnosis of orbital infarction. Notably, other case reports have diagnosed orbital infarction without mentioning osteal findings [17-20]. Another report describing orbital swelling in sickle cell disease found no initial bony changes on CT imaging in the setting of sickle cell-associated orbital swelling; however, two days later, the patient developed a cephalohematoma with evidence of extra-orbital frontal bone infarction on MRI and scintigraphy [5]. We were unable to find another case of suspected orbital infraction that reported no bone abnormalities on imaging (Table 1). Some authors have postulated that scintigraphy may be required to visualize the bony infarction in some cases [1]. Because of this, we believe our case may represent early orbital ischemia with associated edema.

Once identified, standard vaso-occlusive crisis management often leads to clinical improvement; resolution appears to be expedited by the administration of corticosteroids, again portending inflammatory-mediated post-infarctive edema[1, 13, 18]. In cases of large hematomas, surgical drainage may be required to prevent vision loss[1, 13, 18]. Our patient's symptoms resolved rapidly following conservative sickle cell management paired with antibiotics, further purporting orbital infarction as a likely etiology.

CONCLUSION

Orbital swelling in sickle cell disease is a multifaceted diagnosis requiring thorough history, exam, laboratory and imaging studies. Our differential was complicated by physical exam findings purulent discharge; insufficient imaging to suggest a bony abnormality; and the healthcare climate of the coronavirus pandemic. Because initial treatment included broad-spectrum antibiotics in tandem with analgesia and hydration for vaso-

occlusive crises, the team was unable to isolate the treatment responsible for clinical improvement. Other cases of orbital infarction report similar confusion, as the presentation and imaging often mimic an infectious process of the orbital soft tissue. Together, this case may provide another example of the complicated presentation of bilateral orbital bone infarction.

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Table 1. Demographics, clinical, and imaging characteristics of orbital infarction case reports from 2010-2020

First Author	Age (y)	Sex	SCD Genotype	Laterality	Proptosis ± Pain/ Tenderness	Reduced Motility	Visual Acuity Changes	CT or MRI Orbit, Brain	Stated Bone Abnormality	Initial Diagnosis
Alghamdi (2018)	12	M	HbS-β thal	R	Proptosis, pain	Superiorly	Diplopia 20/30 (R)	Periorbital edema, R lateral wall mass (superior subperiosteal hematoma) (MRI) Abnormal bone marrow signals (orbital wall infarction) (MRI)	Yes	Orbital infarction
Al Somali (2020)	18	M	HbSS	Bilateral (L > R)	Absent	Absent	Absent	Bony infarctions and subperiosteal hematomas within bilateral frontoparietal regions Extraconal hematoma to superior lateral orbital wall with mass effect to lacrimal gland and L LR muscles	Yes	Orbital infarction
Alsuhaibani (2011)	11	M	HbSS	R	Proptosis, pain, tenderness	Superiorly Laterally	Absent	R subperiosteal lateral orbital wall collection (CT) Greater sphenoidal wing marrow infarction with subperiosteal collection and ring enhancement (MRI)	Yes	Orbital infarction (OCS)
Edmunds (2017)	5	M	HbSS	R	NS, pain	Absent	Absent	R superolateral orbital fluid collection (CT)	No	Orbital cellulitis
Ghafouri (2011)	2	M	HbSS	Bilateral	NS, absent	Mildly limited abduction bilaterally	NS	Bilateral subperiosteal lateral orbital fluid collections causing deviation of LR muscles Non-enhancement of lateral orbital wall, sphenoid triangles, and clivus suggesting prior bone infarction (MRI)	Yes	NS
Helen (2013)	11	F	HbSS	Bilateral (R > L)	Proptosis, pain	Complete immobility	No light perception	Bilateral proptosis, bullous retinal detachment, subretinal fluid collection (US) No orbital collection, mass, intracranial extension (CT)	No	Orbital cellulitis
Ilhan (2014)	15	M	HbSS	Bilateral (R > L)	NS	R reduced (direction NS)	Absent	R orbital superolateral subperiosteal hematoma (CT) R frontal epidural hematoma (CT)	No	Orbital infarction (OCS)
Janssens (2015)	17	M	HbSS	Bilateral (L > R)	Proptosis (L), absent	Absent	Absent	L periorbital edema (MRI) L orbital wall bone abnormalities extending to intra-orbital with L LR involvement (MRI)	Yes	NS
McBride (2016)	5	M	NS	R	Proptosis (R), absent	Superiorly	Diplopia 20/30 (R) 20/25 (L)	R rim-enhancing superolateral orbital fluid collection displacing orbital contents (CT) Diffuse fat stranding in R eyelids extending into facial soft tissues (CT)	No	Subperiosteal hemorrhagic effusion
Schündeln (2014)	8	M	HbSS	Bilateral	Proptosis, pain	Laterally	No	Bilateral lateral orbital cavity hematoma with dislocation of bilateral LR (MRI)	No	Orbital infarction (OCS)
Sundu (2017)	14	M	NS	Bilateral (L > R)	Proptosis, pain	Superiorly Laterally	16/20 (L)	Calvarial frontal and parietal bone infarction (MRI) Bilateral subperiosteal orbital wall hematoma (MRI)	Yes	Orbital infraction (OCS)
Van de Voorde (2019)	19	M	HbSS	L	Proptosis (L), absent	Absent	Absent	L lateral orbital wall subperiosteal orbital hematoma (extraconal mass with high attenuation [CT], hypointense with fat suppression [T2], isointense with adjacent bone [T1]) L frontal bone subperiosteal hematoma (MRI) L frontal/L greater wing infarction (discrete edema [T2], asymmetric low-signal intensity [T1])	Yes	Orbital infarction