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Tired and Swollen: A Mono Mimic for Angioedema

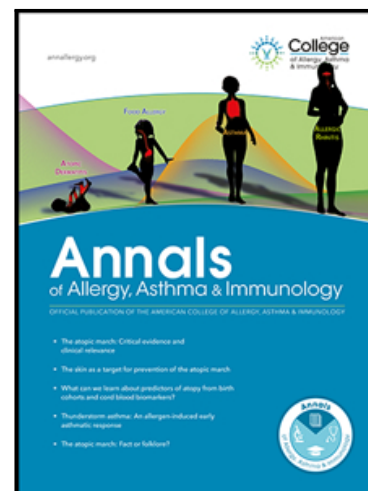
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Title Page

1. Title: Tired and Swollen: A Mono Mimic for Angioedema
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- Infectious mononucleosis (IM) secondary to Epstein-Barr virus (EBV) infection classically presents as a triad of cervical lymphadenopathy, fever and pharyngitis¹ that is often accompanied by persistent fatigue. An uncommon presentation of early IM that

has been reported rarely in the literature is periorbital edema. Here, we present a case of a 19 year-old female referred to allergy clinic for evaluation of angioedema. She was found to have periorbital swelling mistaken for angioedema and ultimately was diagnosed with IM despite lacking symptoms of the classic triad. Our case highlights the differential diagnosis of periorbital edema and alerts clinicians that IM should be considered in particular for young adult and adolescent patients.

A 19 year-old previously healthy female was referred for evaluation of angioedema. She described a 3-week history of recurrent bilateral periorbital swelling. Episodes would persist for about 3 days with spontaneous resolution for 1 day followed by recurrence. Neither her conjunctivae nor eyelids were painful or pruritic. She experienced no desquamation, changes in vision or ophthalmoplegia. She could anticipate when the swelling would occur due to preceding skin tenderness and the appearance of dark rings around her eyes. She denied new topical exposures, environmental changes, pharyngitis, lymphadenopathy, fevers, chills, cough, nasal congestion, joint pains, night sweats or weight loss. She did however endorse mild to moderate fatigue that coincided with the timeframe of periorbital swelling. On presentation, patient was afebrile with normal vital signs. Physical exam revealed bilateral periorbital edema, violaceous discoloration of her eyelids and no injection of the conjunctiva. Her oropharynx was clear and there was no appreciable lymphadenopathy. Complete blood count, basic metabolic panel, liver panel, inflammatory markers, tryptase, basophil activation assay, complement, protein electrophoresis and thyroid studies were normal. Heterophile antibody testing was positive for mononucleosis. Her

symptoms of fatigue and swelling resolved within days of the evaluation without further sequelae.

Our report provides an informative and illustrative case for the practicing allergist presented with the common clinical concern of angioedema. Upon review, our patient lacked the characteristic features of non-pitting, asymmetric, distorting swelling to support the diagnosis.

Our patient's predominant symptom was symmetric periorbital edema thus redirecting the evaluation to other possible culprits. Given the lack of pruritis, skin desquamation and reliable trigger, immediate hypersensitivity reactions and contact dermatitis were deemed unlikely. Our patient also lacked conjunctival injection, discharge and any vision changes concerning for localized infection. We next considered other possible systemic disorders associated with swelling and fatigue. Her laboratory testing showed no abnormalities to support myxedema or nephrotic syndrome. The physical exam did raise the question of a heliotrope rash however the absence of target organ complaints such as weakness, myalgias or arthralgias were not consistent with dermatomyositis. Similarly, the normal inflammatory markers (ESR, CRP) and complement profile were not suggestive of autoimmune disorders such as systemic lupus erythematosus (SLE). Given her fatigue, age and position as a university student, our suspicion for infectious mononucleosis as the cause for her swelling was heightened prompting inclusion of heterophile testing in the evaluation.

Infectious Mononucleosis (IM) is a viral disease most often secondary to EBV infection¹. IM classically presents as a triad of cervical lymphadenopathy, fever and pharyngitis frequently accompanied by lingering fatigue. Upon primary infection, 75% of young adults between the ages of 18-22 develop symptoms typical of IM while 15% present with atypical symptoms and 10% remain asymptomatic².

Periorbital edema has been reported as a rare early manifestation of IM³ though the literature is sparse. A review of the current literature revealed 6 case reports regarding this topic. In these cases, patients ranged from the ages of 8 to 29 and experienced bilateral periorbital swelling along with at least 1 of the symptoms of the classic triad. In 2 of the cases, the edema preceded the symptoms of the classic triad^{4,5} while in the rest of the cases, the edema came about concurrently or after the development of the classic symptoms^{6,7}. About half of the cases also commented on the presence of atypical lymphocytosis, elevated CRP levels, and mild transaminitis^{5,6,7,8}. Each case had serologic confirmation of EBV infection with the presence of anti-VCA IgM.

Our case serves to highlight the broad spectrum of IM presentations and support its inclusion in the differential of periorbital edema even in the absence of the classic triad of symptoms, especially if fatigue is present. The periorbital edema typically lacks conjunctivitis, pruritis or pain³ and the swelling has been noted to last from days to weeks^{5,6,7}. The etiology of the edema remains unknown, however it presumably is related to nasopharyngeal replication of virus, lymphoproliferation or lymphatic obstruction³. Of note, our patient also did not have atypical lymphocytosis, elevated CRP levels or transaminitis that were noted in prior case reports.

Our patient did not return as requested for an EBV panel to allow for further serologic confirmation. We do not believe this to be a significant limitation however given that the specificity of heterophile antibody testing has been reported as superior to that of EBV-specific serologies due to significant cross-reactivity of VCA-IgM in cytomegalovirus (CMV) infections.⁹ Viral infections such as CMV, toxoplasmosis, adenovirus and rubella only rarely cause false-positive heterophile antibody tests¹⁰ and would not fit the clinical presentation. Rare false-positives can also occur in patients with SLE, HIV and lymphoproliferative disorders which were able to be excluded given her spontaneous symptom resolution and laboratory work up. Given our patient's clinical course and laboratory data, it is reasonable to conclude that the correct diagnosis was IM secondary to EBV.

In conclusion, this report emphasizes the need for physicians to consider IM related to a primary EBV infection when periorbital edema is encountered even in the absence of fever, pharyngitis, and lymphadenopathy. Periorbital edema can invoke concern over disease processes such as hypersensitivity reactions, contact dermatitis, hypothyroidism, nephrotic syndrome, SLE, dermatomyositis, cutaneous sarcoidosis, infection or, as in this case, masquerading as angioedema. Thus recognition of an atypical IM presentation is paramount to the prevention of inappropriate or delayed diagnoses.

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Figure Legend

Figure 1: 19 year-old female with periorbital swelling.



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