EUROPEAN OPHTHALMIC PATHOLOGY SOCIETY

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Summary statement: **Candy crush of the orbit: 49-year-old male with a history of CMML**

Clinical presentation: a 49-year-old male presented at the outpatient hematology clinic with a painful swelling of the left jaw. There was an 18-month history of CMML-1 (CSF3R-mutant) treated with oral Hydroxycarbamide in a palliative setting because of non-eligibility for allo-SCT. The patient's condition progressed rapidly with subsequent left sided conjunctivitis, uveitis and pre- and post-septal cellulitis. The globe became painful with photophobia and impaired vision. CRP was elevated at 154 mg/L. CT and MRI showed a severe pre- and post-septal infiltrating mass with traction to the optic nerve and ischemia suspect for (mycotic) orbital cellulitis. Cultures and molecular tests for bacteria, mycobacteria, fungal and viral infection remained negative. Orbital biopsy showed a sterile neutrophilic necrotizing inflammatory process. Anti-bacterial, -fungal and -viral medication showed no relief. Eleven days after initial presentation an orbital exenteration was performed because of increasing proptosis and clinical deterioration. Fourteen days after presentation, also the right eye showed signs of conjunctivitis. Cultures remained negative and methylprednisolone treatment was initiated with a good clinical response and complete resolution of symptoms three weeks after presentation.
Pathology: orbital exenteration specimen 4,6x4,5x3,0 cm. with extensive necrosis. Histopathology shows massive infiltration of all tissues with neutrophils with abundant karyorrhectic debris and lymphohistiocytic admixture. There is extensive necrosis including all structures of the globe. There are no signs of vasculitis. Special stains are negative for bacterial or fungal infection.
Diagnosis: **Periorbital necrotizing Sweet syndrome**
Discussion: Sweet syndrome is a neutrophilic dermatosis along a spectrum with pyoderma gangrenosum that typically presents acutely with fever and multifocal, tender, erythematous, cutaneous plaques or nodules, often with overlying vesicles first described in 1964.[1] Necrotizing Sweet syndrome was initially described as a distinct variant of Sweet syndrome in 2012.[2] The etiology of Sweet syndrome remains elusive, but the disease process is thought to stem from a cytokine mediated hypersensitivity reaction that may be idiopathic or triggered by an infection, medication, or malignancy.[3] It is therefore classified in 3 forms: classical, malignancy-associated, and drug-induced. The classical, or idiopathic, presentation often occurs after a viral illness, commonly an upper respiratory infection, or in association with another autoimmune disease such as sarcoidosis or erythema nodosum. In paraneoplastic Sweet, hematologic malignancies have been found to be most frequently associated, in particular acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS). In that

spectrum the history of CMML-1 is of importance in the current case. Moreover, this form can also be related to the newly recognized VEXAS syndrome.[4] The most common ocular manifestation is conjunctivitis, but Sweet syndrome can affect all ocular and periorbital tissues.[5] Classic, idiopathic Sweet mostly presents as conjunctivitis, whereas cases of orbital Sweet are mostly paraneoplastic associated with hematologic malignancies.[6-13] Considering the immunocompromised status of these patients and the somewhat overlapping clinical presentation of Sweet syndrome with infection, including fever and leucocytosis with neutrophilia, Sweet syndrome may be misdiagnosed as a skin or soft tissue infection and in the ophthalmic practice with infectious orbital cellulitis.[5-12,14-19] In contrast to most cases of Sweet syndrome, significant tissue necrosis is present with necrotizing Sweet syndrome.[13,20] The acute and rapidly progressive clinical presentation can closely resemble infectious orbital cellulitis such as mucor mycosis requiring acute debridement. Sweet syndrome, as with other neutrophilic dermatoses, however often shows pathergy and is instead treated with corticosteroids and immunosuppression.[5,7,13] In the current case such pathergy reaction may have been the cause of the progression after initial diagnostic biopsy. Histopathology is still helpful for a correct diagnosis: a very dense neutrophilic infiltrate in the absence of microorganisms might lead to reconsider an infectious cause for orbital cellulitis. In angioinvasive fungal infections, hyphae are readily visible on histopathology. In necrotizing fasciitis, initial gram stain is typically revealing, and cultures grow rapidly. The absence of such features should raise alternative differential diagnostic considerations. Since Sweet syndrome is exquisitely steroid responsive, response to a single dose of IV corticosteroids may be considered as diagnostic confirmation.

In conclusion, necrotizing Sweet syndrome is an unusual form of the more commonly encountered neutrophilic dermatoses of classical Sweet syndrome and pyoderma gangrenosum. It is a challenging diagnostic entity due to its overlapping features with necrotizing fasciitis and infectious (mycotic) orbital cellulitis and the rarity of necrosis in Sweet syndrome. It is therefore crucial to maintain a high level of clinical suspicion, especially in the presence of pathergy, characteristic histopathological findings, and largely negative wound cultures.

1. Sweet, R.D. An Acute Febrile Neutrophilic Dermatosis. *Br J Dermatol* **1964**, *76*, 349-356, doi:10.1111/j.1365-2133.1964.tb14541.x.
2. Kroshinsky, D.; Alloo, A.; Rothschild, B.; Cummins, J.; Tan, J.; Montecino, R.; Hoang, M.P.; Duncan, L.; Mihm, M.; Sepehr, A. Necrotizing Sweet syndrome: a new variant of neutrophilic dermatosis mimicking necrotizing fasciitis. *J Am Acad Dermatol* **2012**, *67*, 945-954, doi:10.1016/j.jaad.2012.02.024.
3. Heath, M.S.; Ortega-Loayza, A.G. Insights Into the Pathogenesis of Sweet's Syndrome. *Frontiers in immunology* **2019**, *10*, 414, doi:10.3389/fimmu.2019.00414.
4. Sterling, D.; Duncan, M.E.; Philippidou, M.; Salisbury, J.R.; Kulasekararaj, A.G.; Basu, T.N. VEXAS syndrome (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) for the dermatologist. *J Am Acad Dermatol* **2023**, *89*, 1209-1214, doi:10.1016/j.jaad.2022.01.042.
5. Gottlieb, C.C.; Mishra, A.; Belliveau, D.; Green, P.; Heathcote, J.G. Ocular involvement in acute febrile neutrophilic dermatosis (Sweet syndrome): new cases and review of the literature. *Surv Ophthalmol* **2008**, *53*, 219-226, doi:10.1016/j.survophthal.2008.02.006.
6. Keen, J.A.; Fisher, M.D.; Yu, C.Y.; Swick, B.L.; Shriver, E.M. Elevated Intraocular Pressure in Periorbital Sweet's Syndrome. *Ophthalmic plastic and reconstructive surgery* **2023**, *39*, e115-e117, doi:10.1097/IOP.0000000000002373.
7. Khatri, M.L.; Taha, M. Sweet's syndrome associated with myelodysplastic syndrome presenting as periorbital cellulitis. *Int J Dermatol* **2007**, *46*, 496-499, doi:10.1111/j.1365-4632.2006.03019.x.
8. Li, C.Y.; Rosenblat, T.L.; Husain, S.; Silvers, D.N.; Khandji, A.G.; Ben-Dov, M.; Odel, J.G.; Wesley, S.F. Sweet Syndrome in the Central Nervous System: A Case of Orbital Inflammation, Sixth Nerve Palsy, and Pachymeningitis. *J Neuroophthalmol* **2024**, doi:10.1097/WNO.0000000000002256.

9. Maalouf, T.; Angioi, K.; Ssi-Yan-Kai, I.; Vernerey, F.; Witz, B.; George, J. Dacryoadenitis associated with subcutaneous Sweet's syndrome in a patient with acute myeloid leukemia. *Orbit* **2005**, *24*, 55-57, doi:10.1080/01676830590903562.
10. Morgan, K.W.; Callen, J.P. Sweet's syndrome in acute myelogenous leukemia presenting as periorbital cellulitis with an infiltrate of leukemic cells. *J Am Acad Dermatol* **2001**, *45*, 590-595, doi:10.1067/mjd.2001.119032.
11. Ozcelik, T.; Ozkocaman, V.; Ali, R.; Ozkalemkas, F.; Bulbul-Baskan, E.; Yazici, B.; Ozkan, A.; Tunali, A. Sweet's syndrome: dilemma in febrile neutropenic patient with acute myeloid leukemia. *Leuk Res* **2006**, *30*, 1466-1468, doi:10.1016/j.leukres.2006.01.019.
12. Taravati, P. Neuro-Sweet Disease Causing Orbital Inflammation. *Neuro-ophthalmology (Aeolus Press)* **2015**, *39*, 42-45, doi:10.3109/01658107.2014.961090.
13. Vongsachang, H.; Chiou, C.A.; Azad, A.D.; Lin, L.Y.; Yoon, M.K.; Lefebvre, D.R.; Stagner, A.M. Periorbital necrotizing sweet syndrome: A report of two cases mimicking necrotizing soft tissue infections. *Am J Ophthalmol Case Rep* **2024**, *34*, 102033, doi:10.1016/j.ajoc.2024.102033.
14. Anwar, S.; Hassan, S.; Fern, A.I.; Douglas, W.S.; Mann, B. Bilateral periocular swelling in Sweet's syndrome. *Eye (Lond)* **2004**, *18*, 214; discussion 214-216, doi:10.1038/sj.eye.6700588.
15. Baartman, B.; Kosari, P.; Warren, C.C.; Ali, S.; Jorizzo, J.L.; Sato, M.; Kurup, S.K. Sight-threatening ocular manifestations of acute febrile neutrophilic dermatosis (Sweet's syndrome). *Dermatology* **2014**, *228*, 193-197, doi:10.1159/000357729.
16. Bulengo-Ransby, S.M.; Brown, M.D.; Dubin, H.V.; Rasmussen, J.E.; Nickoloff, B.J. Sweet's syndrome presenting as an unusual periorbital eruption. *J Am Acad Dermatol* **1991**, *24*, 140-141, doi:10.1016/s0190-9622(08)80050-3.
17. Gupta, N.; Chawla, B.; Venkatesh, P.; Tandon, R. Necrotizing scleritis and peripheral ulcerative keratitis in a case of Sweet's syndrome found culture-positive for Mycobacterium tuberculosis. *Ann Trop Med Parasitol* **2008**, *102*, 557-560, doi:10.1179/136485908X311812.
18. Jang, Y.; Jang, K.; Kim, N.; Khwarg, S.I.; Choung, H.K. Blindness in Sweet's Syndrome. *Korean J Ophthalmol* **2017**, *31*, 570-571, doi:10.3341/kjo.2017.0084.
19. Tsoutsanis, P.; Kapantais, D. Orbital apex syndrome secondary to Sweet syndrome. *BMJ Case Rep* **2025**, *18*, doi:10.1136/bcr-2024-262085.
20. Watson, S.L.; Kuo, A.; Kishi, S.H.; Fat, M.N.; Boxrud, C.A. Periorbital Necrotizing Sweet's Syndrome: A Case Report. *Ophthalmic plastic and reconstructive surgery* **2023**, *39*, e197-e199, doi:10.1097/IOP.0000000000002463.

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Summary:
A 49-year-old man with CMML-1 presented with painful left jaw swelling that progressed to severe orbital inflammation and vision loss. Despite broad-spectrum antimicrobial therapy, his condition worsened, and cultures remained negative. Imaging showed an infiltrative orbital mass, and biopsy revealed sterile neutrophilic necrosis without infection. An orbital exenteration was performed due to clinical deterioration. Later, symptoms appeared in the right eye but resolved rapidly with corticosteroids. Histopathology confirmed **necrotizing Sweet syndrome**, a rare and aggressive neutrophilic dermatosis associated with hematologic malignancies. Early recognition is critical, as it mimics severe infections but responds well to steroids.