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急性髓系白血病相关Sweet综合征一例

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摘　要

目的：探讨急性髓系白血病相关急性发热性嗜中性皮病的临床特征及诊治。方法：报道1急性髓系白血病相关Sweet综合征分析其临床特点及诊疗经过，复习国内外相关文献。结果：62岁女性患者，因高热1月，皮肤红斑伴破溃半月住院，根据症状、辅助检验、皮肤学活检考虑为急性发热性嗜中性皮病，给予激素治疗后皮疹好转，出现血小板低，行骨髓穿刺见2%的原始细胞，患者拒绝再次骨髓穿刺，血液病诊断无法明确。出院后规律随诊，监测血小板计数均正常，给予激素控制皮疹。7月后，因发热及新发皮疹、四肢无力4天再次入院。因血小板低第二次骨髓穿刺：骨髓中见40.1%的异常髓系原始细胞群，表达MPO，考虑急性髓系白血病，化疗过程中患者很快出现急性重症肺炎(卡氏肺孢子虫感染)，后继发多脏器衰竭死亡。结论：急性髓系白血病相关Sweet综合征患者长期使用激素免疫力低，对肿瘤原发病治疗的耐受性差，预后不佳。应尽早多次骨髓穿刺明确诊断，早期启动原发病的治疗。

关键词

急性发热性嗜中性皮病，急性髓系白血病，糖皮质激素

A Case of Sweet Syndrome Associated with Acute Myeloid Leukaemia

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Abstract

Objective: To investigate the clinical features and treatment of acute myeloid leukemia-associated acute febrile neutrophilic dermatosis. Methods: One case of acute myeloid leukemia-associated Sweet's syndrome was reported, and its clinical features and diagnosis and treatment were analyzed, and the relevant domestic and foreign literature was reviewed. Results: A 62-year-old female patient was hospitalized with high fever for one month and erythema with broken skin for half a month. Based on the symptoms, auxiliary tests and dermatological biopsy, she was considered to have acute febrile neutrophilic dermatosis, and her rash improved after glucocorticoid treatment, low platelets were present, 2% of the original cells were found in bone marrow puncture, and the patient refused to repeat bone marrow puncture, so a definitive diagnosis could not be made. The patient was discharged from the hospital with regular follow-ups and normal platelet counts, and was given glucocorticoid to control the rash. 7 months later, she was readmitted to the hospital with fever, new rash, and weakness of the limbs for 4 days. A second bone marrow puncture was performed because of low platelet count: 40.1% abnormal myeloid progenitor cells were found in the bone marrow, expressing MPO, and acute myeloid leukemia was considered, and the patient soon developed acute severe pneumonia (*Pneumocystis carinii* infection) in the course of chemotherapy, and died of multiple organ failure later on. Conclusion: Patients with Sweet syndrome associated with acute myeloid leukemia have low immunity because of long-term glucocorticoid use, poor tolerance to the treatment of the primary tumor, and poor prognosis. Multiple bone marrow punctures should be performed as early as possible to clarify the diagnosis and initiate the treatment of the primary tumor at an early stage.

Keywords

Acute Febrile Neutrophilic Dermatosis, Acute Myeloid Leukemia, Glucocorticoid

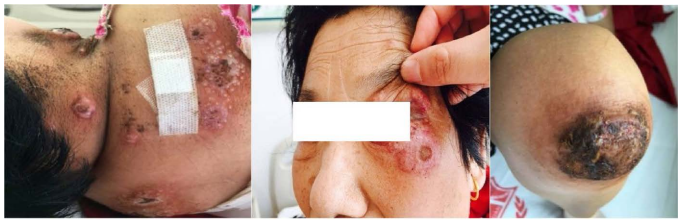
1. 引言

急性发热性嗜中性皮病(acute febrile neutrophilic dermatosis)，又称 Sweet 综合征(SS)是一种异质性炎症皮肤病，其组织病理学特征为无菌性、以中性粒细胞浸润为主[1]。SS 典型特征是突然出现疼痛性红斑，或真皮内以中性粒细胞浸润为主的结节，好发于 47~57 岁之间，女性多于男性，可分为经典型、恶性肿瘤相关型和药物诱导型，糖皮质激素为治疗的首选药[1]。糖皮质激素可以有效减轻炎症和缓解症状[2]。但糖皮质激素会升高红细胞、血小板、中性粒细胞计数，降低淋巴细胞数量，导致患者免疫力低下[3]。恶性相关 SS (MASS)占 SS 的 15%~20%，其中急性髓系白血病(AML)是最常见的相关恶性肿瘤[4]。急性髓系白血病(acute myeloid leukemia, AML)一种恶性克隆性疾病，以髓系原始细胞克隆增殖，丧失髓系祖细胞分化，导致无效的正常造血，使其免疫力低下[5]。老年急性髓系白血病相关 Sweet 综合征前期未能及时确诊的情况下使用激素治疗会使其后期对肿瘤原发病治疗的耐受性差，更易导致真菌的感染，预后不佳。本文回顾性分析青岛大学附属医院风湿科收治的 1 例急性髓系白血病相关 Sweet 综合征患者的患者，对其诊治经过及预后进行探讨，对急性髓系白血病相关 Sweet 综合征的早期诊断及激素使用提供参考。

2. 病历资料

2.1. 病历简介

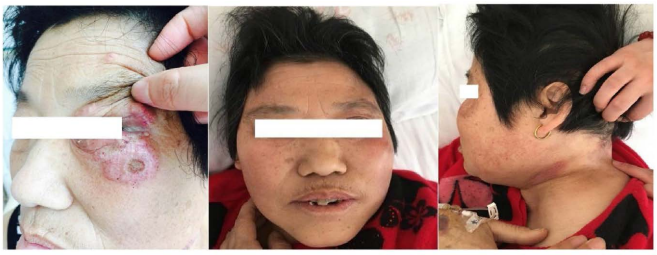
患者，女，62 岁，因高热 1 月，皮肤红斑伴破溃半月于 2019.8.17 第一次入院。既往糖尿病。入院体征：颈背部、左膝皮肤隆起样红斑、结节，大者约 7 × 7 cm，表面见脓疱，部分红斑破溃结痂，左眼颞侧巩膜充血性结节(图 1)。实验室检查：血红蛋白 88 g/L，血小板 102 × 10^9/L，C 反应蛋白 152 mg/L，ESR 116 mm/h，铁蛋白 > 2000 ng/ml，ANCA、ANA、ENA 均阴性。皮肤活检病理：(后颈部皮肤)部分区域表皮脱失，真皮乳头水肿，真皮上中层密集的中性粒细胞浸润，符合 Sweet 综合征。诊断急性发热性嗜中性皮病，给予甲强龙 40 mg/d，皮疹改善不明显，仍有间断发热，将甲强龙加量至 60 mg/d，后患者未再发热，皮疹逐渐结痂(图 2)。激素减量至甲强龙 12 mg bid，复查血红蛋白 79 g/L，血小板 78 × 10^9/L，考虑不除外血液病，于 2019.9.1 骨髓涂片：明显增生骨髓象，粒红比倒置，巨核数少，血小板较少见。骨髓血液肿瘤免疫分型：骨髓中见 2%的原始细胞。建议患者换部位骨髓穿刺，患者拒绝，于 2019.9.8 出院。出院后门诊规律随诊半年，复查血小板均正常，激素逐渐减量至甲强龙 8 mg/d，血糖控制不佳。2020.3.22 患者因发热及新发皮疹、四肢无力 4 天再次入院。实验室检查：白细胞 17.01 × 10^9/L，单核细胞 10.56 × 10^9/L，血小板 43 × 10^9/L。于 2020.3.29 第二次骨髓穿刺，骨髓血液肿瘤免疫分型：骨髓中见 40.1%的异常髓系原始细胞群，表达 MPO，根据流式免疫分型倾向考虑急性髓系白血病(M2 可能)。



(a) (b) (c)

(a) 颈背部皮疹(治疗前)；(b) 左眼巩膜及眼周皮疹(治疗前)；(c) 左膝部皮疹(治疗前)。

Figure 1. Prior treatment
图 1. 治疗前



(a) (b) (c)

(a) 左眼巩膜及眼周皮疹(治疗中)；(b) 面部皮疹(治疗后)；(c) 颈背部皮肤(治疗后)。

Figure 2. Post treatment
图 2. 治疗后

2.2. 诊断

急性髓系白血病，肿瘤相关性 Sweet 综合征，糖尿病。

2.3. 治疗及随访

于 2020.4.2 转入血液科，行地西他滨、高三尖杉酯碱、阿糖胞苷联合方案化疗，过程中患者出现急性重症肺炎(卡氏肺孢子虫感染)，后继发多脏器衰竭于 2020.4.16 死亡。

3. 讨论及文献复习

1964 年 Robert Douglas Sweet 首次描述了 8 例女性患者出现的伴发热及白细胞增多的急性炎症性皮疹,并将其命名为急性发热性嗜中性皮病[6]。该病是由于中性粒细胞增多，广泛浸润真皮浅、中层引起的皮肤疼痛性隆起性红斑,同时伴有发热及其他器官损害,因 Sweet 医生首先报道,又名 Sweet 综合征(Sweet syndrome, SS)。现在根据病因将其分为经典/特发 SS、恶性肿瘤相关的 SS、药物性 SS。

恶性肿瘤相关的 SS 占 SS 病例的很大一部分[7]。它可以是已知肿瘤的伴随表现，也可能是肿瘤的早期表现，或者肿瘤复发的征象[2]。大约 85%的恶性肿瘤相关的 SS 病例有潜在的造血系统肿瘤，包括急性骨髓性白血病、弥漫性大 B 细胞淋巴瘤、霍奇金淋巴瘤、骨髓增生异常综合征和骨髓纤维化；其余 15%与实体恶性肿瘤相关，如泌尿生殖器官癌、乳腺癌和胃肠道癌等[7]。恶性肿瘤相关 SS 的发病机制尚不明确，可能与细菌、病毒、肿瘤或其他抗原引起的免疫反应刺激细胞因子的产生、中性粒细胞活化、浸润以及遗传易感性有关。已经证实多种恶性肿瘤会产生更多的粒细胞集落刺激因子导致白细胞增多[2]。既往报道提示恶性肿瘤相关 SS 的皮肤表现具有某些特点，如出现大疱性溃疡性病变、坏疽性脓皮病，或分布更广泛等[2]。此外，恶性肿瘤相关 SS 患者约 50%存在皮外表现，如贫血、血小板异常、中性粒细胞减少等[8]-[10]。而某些皮肤外表现更可能存在于血液恶性肿瘤中，包括眶周蜂窝织炎、舌头突然肿胀等[11] [12]。与经典 SS 相比，恶性肿瘤相关 SS 更常出现的皮肤病理表现为真皮浅层显著水肿；真皮上中层致密的中性粒细胞浸润，但不浸润表皮；白细胞破碎；内皮肿胀；无血管炎[13]，少数患者可同时表现为皮肤白血病[14]。本例 SS 患者皮肤表现为全身广泛性皮肤及巩膜多发隆起性红斑、结节、脓疱及溃疡，发病时即表现血液系统改变，皮肤病理表现为真皮乳头水肿，上中层中性粒细胞浸润，无血管炎表现。这些表现具有肿瘤相关 SS 特点。

SS 诊断标准：① 突发疼痛性红色斑块或结节。② 组织病理学上真皮层有致密的中性粒细胞浸润，有时可见白血病碎裂性血管炎改变。③ 体温 38℃以上。④ 潜在恶性肿瘤。⑤ 全身糖皮质激素或碘化钾有良效。⑥ 有以下 3 项实验室检查异常，即血沉增快、CRP 升高、白细胞总数 $>8\times10^9$/l，中性粒细胞 >70%。诊断：① + ② + 2/4 (③ + ④ + ⑤ + ⑥) [15]。治疗上，恶性肿瘤相关的 Sweet 综合征目前无统一的治疗指南，对潜在肿瘤治疗时，Sweet 综合征可缓解[16]。但在恶性肿瘤发现前，通常需要全身糖皮质激素治疗[17]。本例患者符合 SS 诊断。大剂量激素治疗后，皮疹缓解，但血液系统异常未能纠正，高度提示血液系统恶性肿瘤可能。第一次骨髓图片见 2%原始细胞，但未进一步追查，失去早期诊断原发病的机会。半年后激素减量至小剂量时皮疹复发，白细胞升高、血小板减少。再次给予大剂量激素，治疗反应差，骨髓穿刺病理示急性髓系白血病(M2)，明确诊断为急性髓系白血病相关 SS。

患者行原发病治疗时表现为对化疗耐受性极差，于首次化疗时出现重症肺炎，继发多脏器功能衰竭，最终死亡。分析该患者死因，卡氏肺孢子虫感染提示患者免疫功能低下，可能与患者长期使用激素及同时患糖尿病，免疫细胞增生及功能低下，以及基础状态差相关，提示早期启动原发病治疗的重要性。

4. 结论

本例患者诊治过程及转归，患者具有临床反复发作、皮肤受累重且有黏膜及下肢皮疹，有白细胞减少、贫血、血小板减少等不典型血液系统表现、激素依赖的特点，应高度警惕血液疾病，以提高对肿瘤原发病治疗的耐受性，改善总体转归。

声　明

该病例报道已获得病人的知情同意。

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