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Case report

Not So Sweet Sweet's Syndrome: A Case of Acute Febrile Neutrophilic Dermatosis in the Treatment of Ovarian Carcinoma

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ABSTRACT

Background: Acute febrile neutrophilic dermatosis, or Sweet's Syndrome (SS), was first characterized by Dr. Robert Sweet in 1964 with eight cases of fever, neutrophilic polymorphonuclear leukocytosis, dermatological lesions, and histological evidence of dense dermal infiltration by mature neutrophils. SS presents in three settings: idiopathic, malignancy-associated, and drug-induced. In 1996, Walker and Cohen outlined the current diagnostic criteria for drug-induced SS with abrupt onset of painful lesions, dermal histology showing dense neutrophilic infiltrate, pyrexia > 38 °C, temporal relationship of drug administration to clinical presentation, and symptom resolution following drug withdrawal or systemic corticosteroid treatment. SS has rarely been reported in association with gynecologic malignancies.
Method: Case Report.
Case: A 41-year-old female receiving neoadjuvant chemotherapy for advanced high-grade serous ovarian carcinoma presented for evaluation of cyclic fevers with dermatologic lesions following treatment with Carboplatin and Taxol, with Pegfilgrastim. On days 11–17 of treatment she reported fevers ranging from 101°F-104°F (38 °C-40 °C) with subsequent eruption of truncal erythematous, pustular, and painful coalescing plaques. Lesion biopsies confirmed histologic presence of dense neutrophilic infiltration. The patient was initiated on oral corticosteroid therapy with symptom improvement.
Discussion: This case represents an example of SS in a patient receiving therapy with the most commonly implicated medication class, granulocyte colony-stimulating factor (GCSF). In drug-induced SS, there's often a temporal relationship between medication administration and symptom development. In this case, all criteria for drug-induced SS were met with a GCS-F as the likely causative agent. This case illustrates a rare diagnosis in the context of gynecologic cancer treatment and will expand available reports of SS in the Gynecologic Oncology literature. We hope to elicit more prompt recognition and diagnosis of SS from practitioners to minimize patient morbidity and long-term sequelae.

1. Introduction

Acute febrile neutrophilic dermatosis, or Sweet's Syndrome, was first characterized by Dr. Robert Sweet in 1964 when he described eight cases of women who presented with a specific set of features including fever, neutrophilic polymorphonuclear leukocytosis, raised dermatological plaques often localized to the face, neck, and limbs, as well as histological evidence of dense dermal infiltration by mature neutrophils. The condition appears to be a reactive phenomenon that often acts as a cutaneous marker of a systemic disease or other process (Fader et al., 2012). Since its first description, multiple reports in the literature have come out associating the phenomenon with infections, pregnancy, autoimmune diseases, drugs, and malignancies (Cohen et al., 1993). Approximately 21% of Sweet's Syndrome cases observed appear to be associated with hematologic or solid tumor malignancies (Cohen et al., 1988). The list of conditions and malignancies associated with SS continues to grow, but, reports associating Sweet's Syndrome with gynecologic malignancies are sparse in the literature (Fader et al., 2012; Culp et al., 2004; Nguyen et al., 1983 Aug; Ehrsam et al., 2006; Clark et al., 2017). There is a particular paucity of reports involving malignancy of ovarian origin with only four cases reported. Here we describe a case of pegfilgrastim drug-induced Sweet's Syndrome in a patient being treated

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for high grade serous ovarian carcinoma. We discuss the typical presentation of this syndrome, review the various sub-types, and synthesize the available literature on the dermatosis in the context of gynecologic malignancies.

2. Case

In January of 2020, a 41-year-old Caucasian female presented to the Emergency Department for evaluation of new onset abdominal pain with subsequent imaging revealing bilateral complex adnexal masses, ascites, peritoneal carcinomatosis, and multifocal retroperitoneal adenopathy. Biopsy of an abdominal mass demonstrated metastatic high grade serous carcinoma of Mullerian origin, clinical Stage IIIC. The patient was started on neoadjuvant carboplatin and paclitaxel therapy while inpatient and was dispositioned to outpatient chemotherapeutic care. The patient subsequently had a mild reaction to paclitaxel-infusion, which resolved with prolonged infusion time. At ambulatory follow-up prior to her second cycle, Pegfilgrastim-cbqv was added to the patient's treatment regimen for neutropenia with an absolute neutrophil count of 700. She was eventually transitioned to biologic therapy with pegfilgrastim for failure of the biosimilar agent to increase the absolute neutrophil count. Following the second and third cycles of neoadjuvant chemotherapy with concurrent exogenous granulocyte colony-stimulating factor treatment, the patient began to note episodes of transient and cyclic fevers ranging from 101°F–104°F (38 °C–40 °C) typically starting on day 11 of the cycle and continuing through days 16–17. Lab work was absent for evidence of neutropenia at that time. Repeated infectious work-ups remained negative. In conjunction with the transient fevers, the patient reported cyclic eruptions of raised, erythematous lesions localized to the arms, torso, thighs and legs with "acne"-like eruptions on the patient's face (Fig. 1). Initially, the dermatologic lesions resolved relatively quickly but it was noted that the lesions remained active in duration for longer periods of time with each subsequent cycle. Following the sixth cycle of chemotherapy, the patient endorsed progressively worsening pain and appearance of the coalescing skin lesions. At that time, the lesions were raised, ulcerative, actively weeping and colored red to dark purple with associated surrounding erythema (Fig. 2). The decision was made at that time to pursue hospital admission for further work-up and evaluation. On admission, excisional biopsies were taken of the lesions present on the patient's right thigh. Subsequent pathology findings described dense histologic presence of neutrophilic infiltration (Fig. 3) consistent with the diagnosis of Sweet's Syndrome. The patient was started on high-dose steroids at 1 mg/kg daily with cessation of any subsequent fevers and initial improvement in the appearance of her dermal lesions. The patient remained stable within two days of admission and was dispositioned to outpatient therapy with a slow daily taper of high dose oral steroids. Following appropriate therapy and recognition of the syndrome, the patient's lesions continued to regress in subsequent follow-up (Fig. 4) and were noted to be stable in their improvement 8 weeks after initial diagnosis. Two years following diagnosis, the patient continues to manifest faded skin lesions (Fig. 5) as a sequelae of her Sweet's Syndrome, but without other associated symptoms.

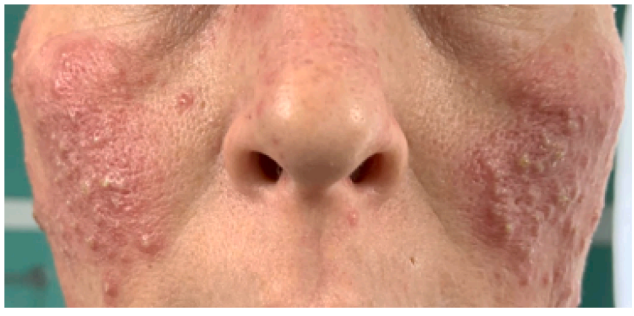

Fig. 1. Facial eruption of erythematous, acneiform lesions.

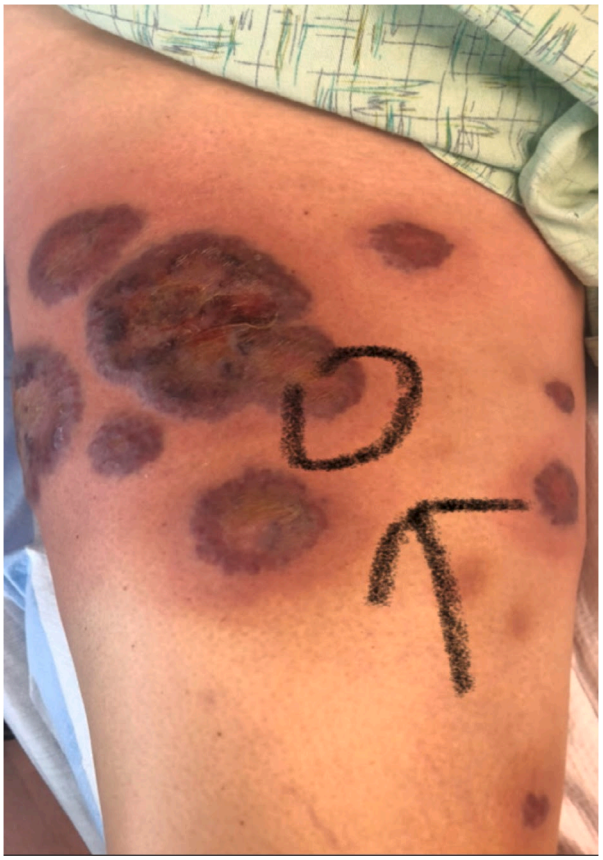

Fig. 2. Truncal, raised, ulcerated lesions on patient's lower extremity.

3. Discussion

The three distinct clinical settings in which Sweet's Syndrome presents include malignancy, drug-induction, and idiopathic settings. A comprehensive review by Cohen et al in 2007 describes in detail the specific characteristics of the Sweet's Syndrome subtypes and specific presentations, risk factors, illness courses, and treatment regimens for each. Based on work done by Cohen and Kurzrock in 1993 (Cohen et al., 1988), malignancy-associated Sweet Syndrome (MASS) is generally accepted to represent roughly 21% of all Sweet's Syndrome cases, with the vast majority of those attributed to hematologic malignancies and with the most common solid tumor malignancies being of the breast, genitourinary tract, and gastrointestinal tract. The classical or idiopathic subtype predominantly affects women (Culp et al., 2004; von den Driesch, 1994) with etiologies thought to be related to infections, inflammatory bowel disease, or pregnancy (Cohen, 2007 Jul). The drug-induced variety of Sweet's Syndrome was first recognized in 1986 secondary to TMP-SMX (Su and Liu, 1986 Mar), but an exhaustive list today would include dozens of medications with pegfilgrastim being the most well-recgonized cause (Raza et al., 2013 May). The number of conditions and medications associated with Sweet's Syndrome continues to expand as it is more frequently recognized and reported by clinicians. While the pathophysiology underlying Sweet's Syndrome is poorly understood, one prevailing theory is related to the presence, mediation, and abundance of cytokines in the body. In addition to cytokines, circulating autoantibodies, dermal dendrocytes, human leukocyte antigen serotypes, and immune complexes may play a role in Sweet's Syndrome developing as a hypersensitivity reaction to an inciting bacterial, viral, or tumor antigen (Cohen, 2007 Jul). When considering malignancy causes, many tumors can not only trigger cytokine production from the

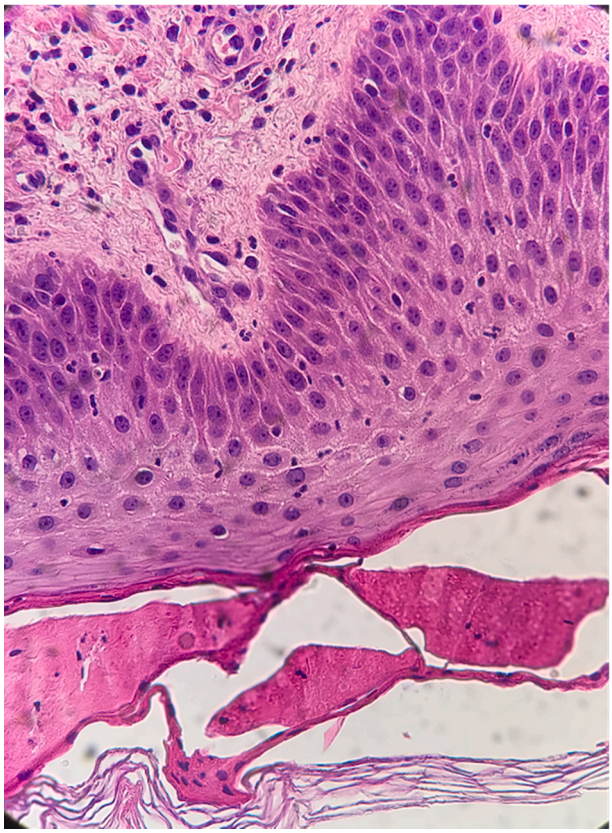

Fig. 3. Dense dermal infiltration by mature neutrophils on histopathology of the patient's lesion biopsy.

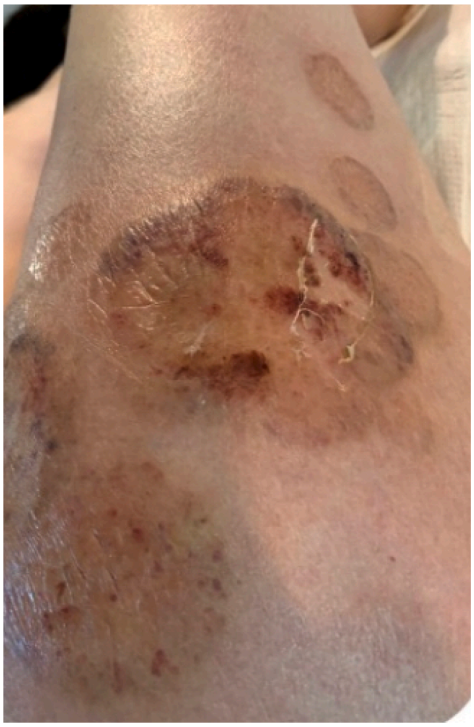

Fig. 4. Appearance of truncal lesions one week after initiating glucocorticoid therapy.

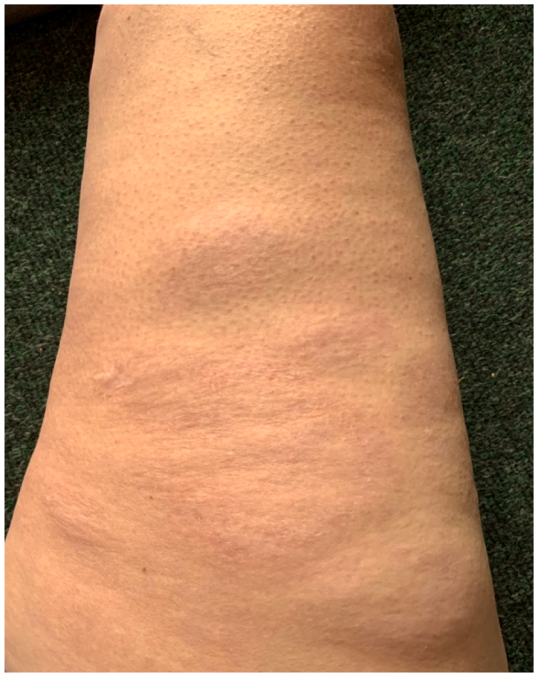

Fig. 5. Chronic sequelae of truncal lesions 2 years after diagnosis.

body's immune system but often have an innate ability to produce and release their own cytokines providing a potential mechanism to develop the syndrome.; additionally, neutrophils play a significant role in the pathogenesis of Sweet's Syndrome likely via their prominent role in in vivo cytokine production (Raza et al., 2013 May). The production and accumulation of neutrophils is driven by both exogenous and endogenous granulocyte colony stimulating factor (G-CSF), so it intuitively makes sense that pegfilgrastim, or exogenous G-CSF, is the most commonly recognized medication in cases of drug-induced Sweet's Syndrome. Once identified, all forms of Sweet's Syndrome are typically responsive to mainstay corticosteroid treatment via a once daily dose of 1 mg/kg with most patients achieving symptom resolution and complete steroid tapering within 4 to 6 weeks (Cohen, 2007 Jul). However, the process of identifying the condition can often be time consumptive and result in misdiagnoses and unnecessary treatment (Raza et al., 2013 May). Time from symptoms to diagnosis is often delayed secondary to the condition's rarity, broad differential, and similar presentations to other, more common, infectious etiologies.

The general diagnostic criteria for Sweet's Syndrome were established by Walker and Cohen in 1996 (Walker and Cohen, 1996 May) and consist of the following four criteria: (a) the abrupt onset of painful lesions, (b) dermal histology showing dense neutrophilic infiltrate without evidence of vasculitis, (c) pyrexia $>$ 38 °C, and (d) resolution of the lesions following systemic corticosteroid treatment or withdrawal of a suspected offending medication. With regards to drug-induced Sweet's Syndrome, a fifth criterion necessary for diagnosis is a temporal relationship between the suspected drug's administration to clinical presentation (Walker and Cohen, 1996 May). This case illustrates an example of a patient who experienced recurrent febrile episodes with painful dermal eruptions that manifested while receiving post-chemotherapy treatment with cycles of pegfilgrastim, exogenous G-CSF. Granulocyte colony-stimulating factors comprise the most commonly associated medication class to trigger symptomatic Sweet's Syndrome. The patient's symptoms emerged following administration of the G-CSF which became progressively more pronounced following the second and third cycles thereby demonstrating a clear temporal relationship to the inciting agent. With each passing cycle, time to eruption of lesions following drug induction shortened, time to lesion resolution lengthened, and the total surface area of skin involved progressively

expanded, all potentially indicating an increased sensitivity to the underlying pathophysiologic changes in this case. A working diagnosis of Sweet's Syndrome was made given the symptom history and histologic evidence to corroborate the syndrome. The patient's lesions promptly resolved with the appropriate steroid therapy satisfying the final criterion and officially establishing a diagnosis of Sweet's Syndrome.

To our knowledge, there have been 4 cases reported of Sweet's Syndrome in the context of ovarian carcinoma prior to this case report: two likely as a sign of cancer recurrence (Nguyen et al., 1983 Aug; Ehrsam et al., 2006), one with Sweet's Syndrome as a presenting feature that led to work up revealing cancer (Fader et al., 2012), and one temporally related to medication administration of topotecan chemotherapy (Dickson et al., 2013 Jan), Sweet's Syndrome has also been reported in the context of non-ovarian gynecologic malignancies; the majority of cases have been identified in the setting of cervical cancer (Clark et al., 2017).

Although Sweet's Syndrome can manifest in the setting of underlying or recurrent malignancies, the temporal relationship of the dermal lesions with GCSF administration and their prompt resolution following steroid therapy in our patient's case indicates a strong preference of drug-induced over malignancy-associated Sweet's Syndrome. Literature describing the settings in which Sweet's Syndrome exists continues to expand, with this report being the first to describe pegfilgrastim's role in the development of drug-induced Sweet's Syndrome in the setting of ovarian carcinoma.

Although Sweet's Syndrome is a relatively rare condition, our contribution to the known literature highlights the importance of correct and prompt diagnosis of the syndrome in the field of Gynecologic Oncology. In specific settings, timely diagnosis of Sweet's Syndrome can appropriately prompt exploration for undiagnosed tumors or raise suspicion for potential occult malignancy. If a patient's history is concerning for drug-induced causes, prompt syndrome diagnosis can lead to swifter clinical resolution with appropriate corticosteroid therapy or cessation of the offending agent. It is important to note that systemic glucocorticoid therapy is considered first-line and highly effective in the treatment of Sweet's Syndrome. We observe that among other gyn-malignancy associated cases of Sweet's Syndrome, there is not a significant consensus on the length of time to resolution or quality of resolution following glucocorticoid therapy. In two of the cases, the patients passed away closely to the time of diagnosis and thus long-term assessment of their sequelae is not available. Another case reported improvement within a few days of therapy but does not discuss long term follow-up. Fitzgerald et al. did remark that if patients are left untreated, they often will have spontaneous resolution of their symptoms within 6–8 weeks. More additions to the literature for Sweet's Syndrome in the context of gyn malignancies would warrant further opportunity to qualify the post-treatment sequelae of patients who are diagnosed. Alternative first-line therapies that physicians should be aware of include colchicine, dapsone, and potassium iodide and should be considered if a patient's combordities preclude the use of systemic glucocorticoid therapy (Maillard et al., 1999; Amouri et al., 2016 Sep; Cohen and Kurzrock, 2002). A better understanding of the pathophysiology of presentation of Sweet's Syndrome by clinicians who may encounter the condition can intuitively lead to quicker diagnosis and subsequent treatment initiation while avoiding unnecessary pharmacological exposure and expensive laboratory testing related to incorrect alternative diagnoses.

CRediT authorship contribution statement

Samantha Haikal: Writing – review & editing. **Tyler Morgan:** Writing – review & editing. **Reeya Patel:** Writing – review & editing. **Gary Gerstner:** Writing – review & editing. **Rebecca Byler Dann:** Writing – review & editing.

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.

References

Fader, A.N., Winder, A.D., Sandadi, S., DeBernardo, R., 2012. Sweet's syndrome: a cutaneous harbinger of ovarian carcinoma. J. Gynecol. Oncol. 23 (4), 288. https://doi.org/10.3802/jgo.2012.23.4.288.

Cohen, P.R., Holder, W.R., Tucker, S.B., Kono, S., Kurzrock, R., 1993. Sweet syndrome in patients with solid tumors. Cancer 72 (9), 2723–2731.

Cohen, P.R., Talpaz, M., Kurzrock, R., 1988. Malignancy-associated Sweet's Syndrome: review of the world literature. J. Clin. Oncol. 6 (12), 1887–1897. PMID: 3058878.

Culp, L., Crowder, S., Hatch, S., 2004. A rare association of Sweet's syndrome with cervical cancer. Gynecol. Oncol. 95 (2), 396–399.

von den Driesch, P., 1994. Sweet's syndrome (acute febrile neutrophilic dermatosis). J. Am. Acad. Dermatol. 31, 535–556.

Cohen, P.R., 2007 Jul. Sweet's syndrome–a comprehensive review of an acute febrile neutrophilic dermatosis. Orphanet J. Rare Dis. 26 (2), 34. https://doi.org/10.1186/1750-1172-2-34. PMID: 17655751; PMCID: PMC1963326.

Su, W.P., Liu, H.N., 1986 Mar. Diagnostic criteria for Sweet's syndrome. Cutis 37 (3), 167–174. PMID: 3514153.

Raza, S., Kirkland, R.S., Patel, A.A., Shortridge, J.R., Freter, C., 2013 May. Insight into Sweet's syndrome and associated-malignancy: a review of the current literature. Int. J. Oncol. 42 (5), 1516–1522. https://doi.org/10.3892/ijo.2013.1874. Epub 2013 Mar 28 PMID: 23546524.

Walker, D.C., Cohen, P.R., 1996 May. Trimethoprim-sulfamethoxazole-associated acute febrile neutrophilic dermatosis: case report and review of drug-induced Sweet's syndrome. J. Am. Acad. Dermatol. 34 (5 Pt 2), 918–923. https://doi.org/10.1016/s0190-9622(96)90080-8. PMID: 8621829.

Nguyen, K.Q., Hurst, C.G., Pierson, D.L., Rodman, O.G., 1983 Aug. Sweet's syndrome and ovarian carcinoma. Cutis 32 (2), 152–154. PMID: 6617253.

Ehrsam, E., Thomas, P., Marrakchi, S., Mailfer, C., Rotteleur, G., Thomas, P., 2006. Sweet's syndrome associated with ovarian carcinoma. J. Eur. Acad. Dermatol. Venereol. 2, 235–238. https://doi.org/10.1111/j.1468-3083.1993.tb00042.x.

Dickson, E.L., Bakhru, A., Chan, M.P., 2013 Jan. Topotecan-induced Sweet's syndrome: A case report. Gynecol. Oncol. Case Rep. 12 (4), 50–52. https://doi.org/10.1016/j.gynor.2013.01.002. PMID: 24371676; PMCID: PMC3862331.

Clark, A.K., Sarcon, A.K., Fung, M.A., Konia, T., Laurin, E.G., Sivamani, R.K., 2017. Malignancy-associated Sweet syndrome: acute febrile neutrophilic dermatosis associated with recurrence of metastatic cervical cancer. Dermatol. Online J. 23 (4), 13030/qt3vt7n4g8. PMID: 28541876.

Maillard, H., et al., 1999. Colchicine for Sweet's Syndrome. A Study of 20 Cases. Br. J. Dermatol. (1951) 140 (3), 565–566. https://doi.org/10.1046/j.1365-2133.1999.02747.x. Blackwell Publishing.

Amouri, M., Masmoudi, A., Ammar, M., Boudaya, S., Khabir, A., Boudawara, T., Turki, H., 2016 Sep. Sweet's syndrome: a retrospective study of 90 cases from a tertiary care center. Int. J. Dermatol. 55 (9), 1033–1039. https://doi.org/10.1111/ijd.13232. Epub 2016 Mar 9 PMID: 26967709.

Cohen, P.R., Kurzrock, R., 2002. Sweet??s Syndrome: A Review of Current Treatment Options. Am. J. Clin. Dermatol. 3 (2), 117–131.