

observed. This infiltrate was composed of lymphocytes and of abundant mononuclear cells that showed large vesicular nuclei and scant eosinophilic cytoplasm, mimicking small histiocytes.

Immunostaining showed that these cells were strongly positive for CD68KP1, with coexpression of myeloperoxidase (Fig. 2b,c). Immunohistochemical study for cytokeratin cam 5.2 was negative, thus excluding metastatic infiltration (Fig. 2d). Blood and skin biopsy cultures came back negative.

The patient was diagnosed with HSS, probably associated with her medication. Palbociclib was suspended and oral prednisone 1 mg/kg daily was started, which resulted in complete resolution of symptoms. The patient continued treatment with letrozole as monotherapy with no relapse over a follow-up period of 6 months.

The pathogenesis of drug-induced HSS is poorly understood. It has been proposed that in cases of drug-induced HSS, the culprit drug may cause a rise in endogenous levels of granulocyte colony-stimulating factor (G-CSF),³ and idiosyncratic granulocytic maturation arrest may occur in the bone marrow. During the recovery phase from this acute bone marrow insult, elevated endogenous levels of G-CSF may induce release of myeloid precursors from the bone marrow into the skin, resulting in an SS-like reaction, with a histiocytoid inflammatory infiltrate histologically.³

Palbociclib is a first-in-class, highly selective inhibitor of cyclin-dependent kinase (CDK) 4 and CDK6. It is indicated for the treatment of hormone receptor-positive and HER2-negative advanced or metastatic breast cancer, in combination with an aromatase inhibitor as initial endocrine-based therapy.⁴ Palbociclib and other CDK4/6 inhibitors (e.g. ribociclib, abemaciclib) are usually well tolerated. Severe skin reactions (grade ≥ 3) occur in $< 1\%$ of patients and have rarely been reported in the literature.^{4,5} To our knowledge, this is the first report of HSS induced by a CDK4/6 inhibitor.

This case illustrates that HSS can mimic cellulitis, cutaneous infiltration by cancer or lymphangitis carcinomatosa in oncology patients. It should be considered as a possible diagnosis especially if protein kinase inhibitors are being administered.

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Methotrexate combined with omalizumab for difficult to treat urticaria: a further step-up treatment?

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Classically, chronic urticaria has been treated following a stepwise approach in which omalizumab and other immunosuppressants occupy the last step. Omalizumab (OMA) and methotrexate (MTX) have both been used separately for the treatment of urticaria.^{1,2} We believe combination treatment with both agents is a valuable alternative for refractory chronic urticaria and other related diseases such as urticarial vasculitis. We report on two patients who responded to this combination treatment.

Patient 1 was a 53-year-old woman first assessed in January 2007 with a 'hive'-like eruption resolving within 24 h without hyperpigmentation. She also described raised red lines after minimal stroking of her skin. Clinical findings were consistent with chronic spontaneous urticaria (CSU) and symptomatic dermatographism.

A combination of different H1 and H2 antihistamines, montelukast and various forms of UV phototherapy were trialled with little clinical response. In June 2010, azathioprine (AZA) was started at a dose based on thiopurine S-methyltransferase enzyme activity, but it was discontinued after 1 month because of drug-induced neutropenia and hepatitis. In September 2010, subcutaneous MTX was introduced up to a dose of 25 mg once weekly, which significantly reduced the severity of the urticaria symptoms and the number of episodes. During that period, no other adverse effects (AEs) were observed and blood test monitoring remained stable. However, although they were improved, the patient's symptoms were still intolerable and she had to reduce her work hours as activity aggravated the dermatographism. In February 2015, OMA was added alongside MTX and titrated up to a total of 300 mg every 4 weeks. This resulted in notable clinical improvement. In March 2016, a loss of efficacy of OMA was

reported by the patient 3 weeks after the treatment, thus, the dose was increased to 300 mg every 3 weeks. She has now been on the combination of OMA plus MTX for 5 years, with good control of her urticaria and without any drug-related AEs.

Patient 2 was a 58-year-old woman with a history of CSU and angio-oedema since February 2007. She was first assessed in the Photobiology Department in April 2008 because of erythema over the dorsal arms following 3–5 min of sunlight exposure. Monochromator phototesting showed an abnormal urticarial response within the UVA and visible wavebands (335–400 nm) with minimal urticarial dose (MUD) of 4700 mJ/cm at the 365 ± 30 nm (half-maximum bandwidth) waveband (reference range for delayed erythema $\geq 18\,000$ mJ/cm) and dose of 47 000 mJ/cm at the 400 ± 30 nm waveband (reference $\geq 56\,000$ mJ/cm), without abnormal delayed responses. Solar simulator showed an abnormal immediate urticarial response to both UVA and visible light on the dorsal hand. These results were consistent with solar urticaria. Despite investigation, no underlying cause was found so this was diagnosed as idiopathic solar urticaria. Over the years, her solar urticaria fluctuated in severity both clinically and as determined by phototesting.

From 2008 to 2015, the patient took OMA 300 mg every 4 weeks and reported clinical improvement; however, it had to be discontinued due to constipation. AZA was trialled but not tolerated due to nausea. Following this, a 4-day course of high-dose intravenous immunoglobulin was given but it was stopped due to significant leucopenia. Later in 2015, the patient was started on subcutaneous MTX 25 mg/week with good tolerance and she continued it for 1 year; this provided the longest period of disease control. In November 2018, she developed a number of weals on the skin of her arm after sun exposure, which resolved with residual bruising within a few days. The lesions were reproducible by phototesting. Histopathology showed a mixed inflammatory cell infiltrate with red cell extravasation, consistent with leucocytoclastic vasculitis, although there was no fibrinoid necrosis. A diagnosis of urticarial vasculitis induced by sun exposure was made, and she was started on dapsone alongside MTX. Unfortunately, she felt unwell when dapsone was increased to 50 mg once daily. As the only systemic immunosuppressant she had tolerated was MTX, that was continued and OMA was reintroduced in December 2019, at a dosage of 150 mg once monthly in combination with MTX 25 mg once weekly. After 3 months of treatment, the patient reported a significant improvement of quality of life, with better control of the condition and without AEs. Monochromator phototesting to long UVA (365 ± 27 nm waveband) performed on the patient's forearm showed the same MUD (threshold response) as before starting the treatment, but there was a delay in the time to response compared with previous testing.

To our knowledge, this combination of MTX and OMA has not been previously reported for the treatment of urticaria. We believe this is an effective treatment option when faced with refractory and severe chronic urticaria or urticarial vasculitis.

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Monitoring of human herpesvirus 6 infection in the management of drug reaction with eosinophilia and systemic symptoms

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We read with interest the recent article in *Clinical and Experimental Dermatology* by Choudhary *et al.*,¹ reporting a fatal case of acute hepatitis failure as a complication of a teriflunomide-induced drug reaction with eosinophilia and systemic symptoms (DRESS). This hepatitis failure developed after the patient suddenly stopped corticosteroids.

Management of severe DRESS is very challenging. We and others have previously demonstrated that DRESS is a consequence of strong immune responses, which can be a reaction against drugs, but can also be the result of human herpesvirus (HHV) reactivation (mainly HHV-6).² Systemic corticosteroids have been shown to be useful in controlling the immune response; however, they exacerbate HHV reactivations and, when tapered too rapidly, can induce a subsequent uncontrolled immune response with organ failure. Quantification of HHV by PCR should therefore be performed and HHV levels regularly monitored in patients presenting with DRESS to ensure that antiviral drugs are prescribed if required in patients being treated with corticosteroids and/or immunosuppressive drugs.