Approximately 20% of patients present with atypical or variant forms of PR, which are less readily recognized than typical eruptions and may pose a diagnostic challenge. The morphologic characteristics of the eruption may be papular, vesicular, purpuric or hemorrhagic, or urticarial. Very small lesions will be observed in papular PR, and PR with enormous plaques is known as pityriasis rosea gigantea of Darier. A morphologic variant characterized by atypical large patches that tend to be few in number and coalescent has been described. In this variant, commonly referred to as pityriasis circinata et marginata of Vidal or limb-girdle PR, the eruption generally appears in the axillae, the groin, or both, with the trunk and extremities usually spared. A simple classification for atypical pityriasis rosea has been proposed by Chuh and Zawar (Box).

In our patient, the eruption fulfills all 3 essential clinical features (discrete annular lesions, scaling, and peripheral collarette scaling with central clearance on at least 2 lesions), all 3 optional clinical features (relatively truncal distribution, orientation along skin cleavage lines, and herald patch), and none of the exclusional clinical features. This case has clinical features of localized PR, papular PR, and pityriasis circinata et marginata of Vidal. It should also be noted that the involvement of penile and scrotal skin is rarely reported in PR. Physicians should be aware of the wide spectrum of PR variants so that appropriate management and reassurance can be offered.

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**Box. Proposed Diagnostic Criteria for Pityriasis Rosea**

A patient is diagnosed as having pityriasis rosea if:

1. On at least one occasion or clinical encounter, he/she has all the **essential clinical features** and at least one of the **optional clinical features**, and
2. On all occasions or clinical encounters related to the eruption, he/she does not have any of the **exclusional clinical features**.

**The essential clinical features are:**

1. Discrete circular or oval lesions,
2. Scaling on most lesions, and
3. Peripheral collarette scaling with central clearance on at least two lesions.

**The optional clinical features are:**

1. Truncal and proximal limb distribution, with less than 10% of lesions distal to mid-upper-arm and mid-thigh,
2. Orientation of most lesions along skin cleavage lines, and
3. A herald patch (not necessarily the largest) appearing at least two days before eruption of other lesions, noted from patient history or from clinical observation.

**The exclusional clinical features are:**

1. Multiple small vesicles at the center of 2 or more lesions,
2. Two or more lesions on palmar or plantar skin surfaces, and
3. Clinical or serologic evidence of secondary syphilis.

**Cutaneous Hemophagocytosis After Alemtuzumab Injection in a Patient With Sézary Syndrome**

Alemtuzumab, a CD52 monoclonal antibody, is increasingly used for treating advanced cutaneous T-cell lymphomas including Sézary syndrome (SS). While injection site reactions are common, the finding of localized cutaneous hemophagocytosis at the injection site without systemic hemophagocytosis is rare.

**Report of a Case** | A woman in her 60s presented with a 2-year history of SS (clinical stage IVA [T4NXM0B2]). After multiple regimens failed, she was treated with subcutaneous alemtuzumab injections (10 mg each) thrice weekly for 10 weeks and experienced complete remission. However, her disease recurred 7 months after therapy was completed. She restarted treatment with alemtuzumab and 1 month later developed large, tender, indurated plaques on the left lower abdomen and right thigh at her injection sites (Figure, A). Analysis of a right thigh biopsy specimen (Figure, B) showed a deep dermal and subcutaneous...
infiltrate of lymphocytes, histiocytes, and neutrophils consistent with injection site reaction. Numerous histiocytes contained phagocytosed lymphocytes, erythrocytes, and/or neutrophils without features of vasculitis or vasculopathy. Immunohistochemical analysis showed a normal CD4:CD8 ratio of 3:1. The results of blood tests and in situ hybridization assays for Epstein-Barr virus (EBV)–encoded RNA and EBV DNA were negative.

The dose of alemtuzumab was decreased, and then the full dose was resumed with dexamethasone premedication, and finally alemtuzumab therapy was discontinued altogether owing to persistent, painful injection site reaction. The indurated erythematous plaques slowly resolved under treatment with clobetasol, 0.05%, ointment. The patient subsequently started a clinical trial of therapeutic PI-3 (phosphatidylinositol 3) kinase inhibitor.

Discussion | Hemophagocytosis (the engulfment of erythrocytes, their precursors, and occasionally white blood cells by typically benign histiocytes) involves multiple sites (spleen, bone marrow, lymph nodes), usually in association with hemophagocytic syndrome (HPS). Characterized by high fever, cytopenias, liver dysfunction, and coagulopathy, HPS can occur primarily (eg, inherited defects of cellular toxic effects) or secondarily (infections, autoimmune/rheumatologic diseases, and malignant conditions, particularly lymphomas). Secondary HPS may result from dysfunctional cytotoxic T and natural killer cells, leading to excess cytokine production and uncontrolled activation of lymphocytes and histiocytes.

Cutaneous findings are seen in 6% to 65% of HPS cases. Clinically, most present with a nonspecific maculopapular eruption, with occasional purpura, erythroderma, and edema. Skin findings may be specific to the underlying malignant condition (eg, cutaneous lymphoma), manifestations of reactive HPS (ie, jaundice and purpura), or a nonspecific maculopapular eruption. In virus-induced cases, the cutaneous appearance may reflect the underlying cause. Typical histopathologic characteristics include a dermal perivascular lymphohistiocytic infiltrate, nuclear debris, extravasated erythrocytes, and, rarely, hemophagocytosis in skin lesions.

We describe herein a case of localized cutaneous hemophagocytosis in an injection site reaction without evident systemic involvement. To our knowledge, only 4 cases of cutaneous hemophagocytosis have been previously reported, with an underlying condition identified in 3 of these 4 cases (lymphoma, autoimmune disease). A viral trigger was suspected but not confirmed in the fourth case. In all cases, there was no evidence of extracutaneous hemophagocytosis, with the isolated skin findings possibly representing a form of leukocytoclastic vasculitis. Features of vasculitis were not identified in our case.

Peripheral T-cell lymphomas (PTCLs) have also been associated with development of HPS. Reactivation of EBV is thought to play a role, although it is unclear whether EBV-infected malignant T cells initiate HPS or if latent EBV infection predisposes to HPS. The development of HPS was reported in 2 of 14 patients with relapsed or refractory PTCL treated with alemtuzumab and was attributed to EBV reactivation in the setting of PTCL. Alemtuzumab has never been linked to HPS in mycosis fungoides or SS and chronic lymphocytic leukemia (CLL). Recent data have shown that soluble CD52 detected in plasma of patients with CLL can form immune complexes with alemtuzumab. However, an underlying immune complex-mediated mechanism seems unlikely in our case in which the reaction was localized to the injection site and there was no vascular damage. Hemophagocytic syndrome in PTCL is thought to result from cytokine release (interferon-γ, tumor necrosis factor, and interleukin-1) by activated reactive and malignant T cells. While our patient was EBV-negative, we speculate that the alemtuzumab injections induced a similar but localized hyp-
pericytokine response from reactive and possibly malignant T cells, resulting in focal cutaneous hemophagocytosis.

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Chronic Lymphedema in Renal Transplant Recipients Under Immunosuppression With Sirolimus: Presentation of 2 Cases

Report of Cases | Patient 1. A man in his 40s developed chronic renal failure secondary to glomerulonephritis and required renal transplantation. Thirteen years later, he required retransplantation. His medical history was relevant for hypertension, dyslipidemia, and severe ischemic heart disease. His immunosuppressive therapy included prednisone, mycophenolate mofetil, and sirolimus. Eight years after his first transplantation, but only a few months after he began sirolimus treatment, he developed left upper extremity lymphedema on the same arm as the arteriovenous fistula (AVF) used for dialysis. The lymphedema was still present at last follow-up (Figure). Complementary studies such as Doppler ultrasonography and magnetic resonance angiography showed normal findings, and the lymphedema could not be attributed to any cause other than sirolimus. The AVF was tied off; sirolimus treatment was discontinued; and he began acupressure treatment (an alternative medicine technique based on the application of physical pressure to trigger points) with some improvement of lymphedema.

Patient 2. A woman in her 40s developed chronic renal failure secondary to polycystic renal disease and required renal transplantation. Her medical history was relevant for hypertension, hiatal hernia, and temporal lobe epilepsy. Her immunosuppressive therapy included prednisone, mycophenolate mofetil, and tacrolimus. This treatment regimen was changed to prednisone and sirolimus when she developed polyomavirus nephritis a year after transplantation. One year after sirolimus was added to her regimen, she developed chronic lymphedema in her right breast and forearm, the same side of her body as her former AVF. No axillary lymph nodes were found. Mammography, magnetic resonance imaging, skin biopsies of the breast, Doppler ultrasonography, and tumor markers assays were repeatedly performed, and all findings were normal. After malignancy was ruled out, her chronic lymphedema could not be attributed to any cause other than sirolimus. It did not improve during a follow-up of 5 years. Unfortunately, the patient died 8 years after transplantation due to primary central nervous system lymphoma.

Discussion | Adverse effects of mTOR (mammalian target of rapamycin) inhibitors include hyperlipidemia, thrombocytopenia, lymphocele, hernia, delayed wound healing, thrombotic microangiopathy, interstitial pneumonitis, angioedema, edema of the eyelids, and acneiform eruptions. Chronic lymphedema is very rare, and only a few cases have been described in the literature.1-3 To relate this adverse event to the drug, it is necessary to exclude other causes of lymphedema. Therefore a negative family history for lymphedema, no evidence of underlying neoplasm, and

Figure. Left Lower Arm Lymphedema

Lymphedema in patient 1 developed a few months after sirolimus treatment was begun.