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WHEN PRURITUS IS NOT ALLERGY: APPROPRIATE SIGNS OF LYMPHOMA AND OTHER MALIGNANCIES FOR THE COMMUNITY ALLERGIST

Case

A 29-year-old woman presented in 2020 with a several-month history of intense pruritus with neck and truncal rash (**Figure 1A**). During the spring, she reported recurrently to health care with intermittent respiratory symptoms, and persistent fever and sweats. X-ray imaging suggested left sided pneumonia with an effusion, for which she received several courses of antibiotics and eventually underwent thoracentesis in June 2020. Concurrently, she noted nodularity in the skin of her upper back and sternum. Past medical history included scoliosis and anemia, initially thought to be related to iron deficiency, though later testing suggested anemia due to inflammation. She had previously developed cutaneous patches, but without a formal dermatologic diagnosis. Of note, she had a family history of psoriasis.

CT imaging in July 2020 demonstrated diffuse opacities within her right lung with partial collapse of her right upper lobe, bilateral pleural effusions, and extensive soft tissue in the mediastinum encasing various venous structures, the pericardium and heart with small pericardial effusion. Mediastinal mass core biopsy demonstrated nodular sclerosing Hodgkin lymphoma. The patient was treated with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) chemotherapy for six cycles and achieved a complete remission. With treatment, her pruritus and rash resolved within 1-2 months; however, she subsequently developed drug-induced flagellate dermatitis[1], which has slowly faded since treatment completion (**Figure 1B**). She remains in remission at most recent follow up.

Pruritus

Pruritus is a common symptom, with 8%-22% of individuals experiencing chronic pruritus defined as an itch lasting longer than six weeks[2-4]. In a prospective study of patients presenting to an outpatient dermatology clinic with chronic pruritus, 22% were diagnosed with an underlying systemic etiology.[5] With some exceptions, the majority of systemic causes are associated with normal appearing skin. Systemic causes of pruritus are extensive, including renal, hepatic, endocrine, hematologic, and iatrogenic (**Table 1**).

Malignancy is an uncommon etiology of pruritus.[6,7] In a population-based cohort of 8,744 patients with chronic pruritus, compared to age- and sex-matched controls, patients with chronic pruritus had higher rates of alcohol use, smoking, higher

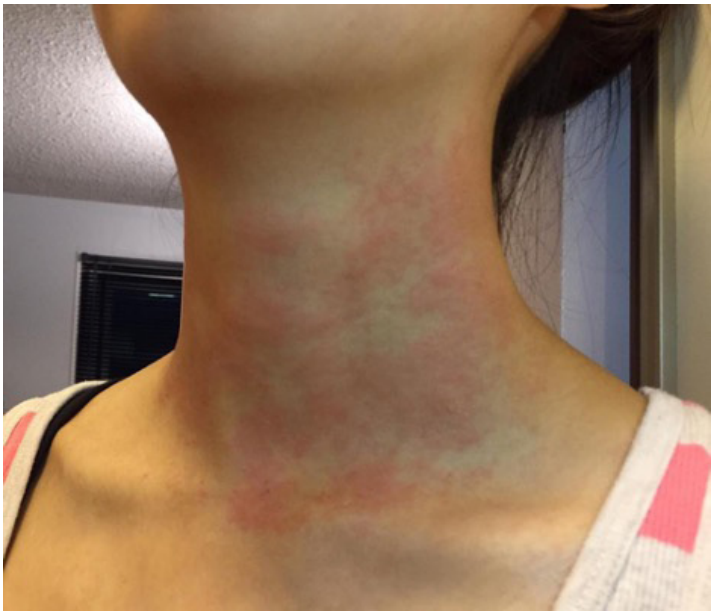

Figure 1A. Demonstration of neck and truncal rash prior to diagnosis; photo courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD

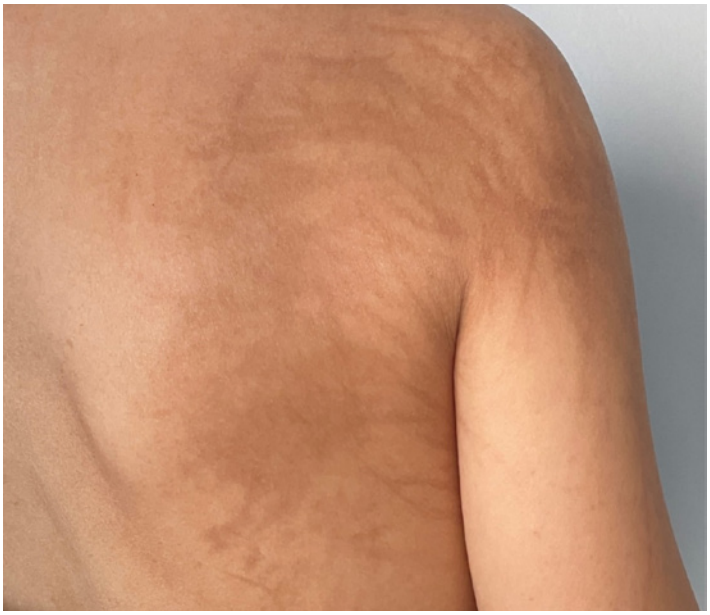

Figure 1B. Hyperpigmentation from bleomycin-induced flagellate dermatitis that developed during treatment with ABVD; photo courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD

System	Specific Disorder
Dermatologic	Xerosis Eczematous dermatitis Urticaria Papulosquamous disorders Infections and infestations Scars
Renal	End-stage renal disease
Liver	Cholestatic liver disease Cholestasis of pregnancy Primary biliary cholangitis
Endocrine	Diabetes mellitus Hyperthyroid Carcinoid syndrome
Hematologic	Myeloproliferative neoplasm (polycythemia vera, essential thrombocytosis, myelofibrosis) Hodgkin lymphoma Non-Hodgkin lymphoma Multiple myeloma Mastocytosis Iron deficiency anemia
Infections	Scabies HIV Varicella Superficial fungal infection Onchocerciasis
Rheumatologic	Sjogren syndrome Scleroderma Dermatomyositis
Neurologic	Brachioradial pruritus Notalgia paresthetica Postherpetic neuralgia Multiple sclerosis
Drug reactions	Examples include: opioids/analgesics, chemotherapeutic agents, chloroquine, antibiotics
Psychogenic itch	
Chronic pruritus of unknown origin	

Table 1. Systemic conditions associated with pruritus; courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD

body mass index and lower socio-economic status. Patients with chronic pruritus also had a higher risk of death[7]. While there was no increase in overall malignancy, increased mortality was attributed to a higher risk of hematologic and bile duct malignancies, HR 2.02 (95% CI 1.48–2.75) and 3.73 (95% CI 1.55 – 8.97), respectively[7]. This study suggests that the search for malignancy in the itching patient should focus on specific etiologies, including hematologic and bile duct malignancies.

Pathophysiology of pruritus in hematologic malignancy

Itch receptors, or polymodal C-fibre nerve endings, are stimulated by pruritogens (e.g., histamine, tryptase, etc) to cause the unpleasant itch sensation.[8] Mast cells and their mediators such as histamine, tryptase, prostaglandins and leukotrienes are involved in the pathogenesis of pruritus.[9] Interleukin (IL)-31 signaling has been identified as central to bridging the immune system with neurons, epithelial surfaces and

connective tissue and plays a role in TH2 mediated pruritus and autoimmune disease.[8] This molecular change is produced by a variety of leukocytes including T cells, eosinophils, basophils, mast cells, monocytes and dendritic cells.[10] In malignancy, there is an increase in pruritogens. For example, mast cells in patients with myeloproliferative disorders release more histamine, leukotrienes and IL-31 compared to those of healthy individuals.[11] In other hematologic malignancies, the cancer cell itself can release histamine, leukopeptidases, bradykinins and IL-31. Additionally, numerous hematologic malignancies can visually involve the skin leading to discomfort, either alone or in combination with systemic disease.

When to consider hematologic malignancy as the cause of pruritus

Table 1 outlines various hematologic diagnoses associated with pruritus. Generalized pruritus is seen in only 1%-3% of patients with non-Hodgkin lymphoma, but in up to 19%-30% of those with Hodgkin lymphoma,[12, 13] occurring more often in the nodular sclerosis subtype. Itch can precede the clinical onset of lymphoma, sometimes described as a burning quality occurring at night, or even precipitated by alcohol consumption. Mycosis fungoides and Sezary syndrome are cutaneous hematologic malignancies associated with itch and rash. A skin biopsy can be helpful in these cases. Aquagenic pruritus, a hot bath- or shower-induced itch, is described in 30%-40% of individuals with a myeloproliferative neoplasm called polycythemia vera (PV). These patients may also present with abdominal symptoms and should have a detailed thromboembolic history as they are at risk of venous and arterial thromboembolism

There are no accepted screening tests for hematologic malignancies. However, routine bloodwork abnormalities may be uncovered. There is a wide spectrum of presentations of hematologic malignancies, ranging from an incidental finding on imaging or routine blood work to an aggressive symptomatic presentation. A symptomatic presentation can include enlarged lymph nodes, symptoms of a mediastinal mass including new cough or shortness of breath, symptoms of splenomegaly including early satiety or abdominal fullness, or constitutional symptoms including recurrent fevers, drenching night sweats or unintended weight loss. A physical examination with specific palpation of cervical, axillary and inguinal lymph nodes regions, and abdominal examination for enlargement of the spleen and liver is recommended.

If history and physical exam are suspicious, or if there has been no cause found, a complete blood count (CBC) and lactate dehydrogenase (LDH) can be helpful. For example, PV is characterized by high hemoglobin levels and can be identified on a CBC. Thrombocythemia can result from reactive or inflammatory causes or relating to a specific mutation such as with the myeloproliferative neoplasms. Some hematologic malignancies such as Hodgkin lymphoma can result in a reactive leukocytosis, predominantly displaying as a left shift or neutrophilia, while some patients may have malignant cells circulating that can be detected on their leukocyte differential. If there is suspicion for hematologic malignancy with a lymphocytosis or abnormal blood cells such as blasts present, flow cytometry testing can be sent on a peripheral blood sample to examine for clonal malignant populations. This test is not useful in the setting of reactive neutrophilia alone, and a blood smear review may help guide decision making. The LDH test can be helpful if elevated and is frequently used in prognostic scores for hematologic malignancy, but should be interpreted with caution as a non-specific test for tissue turnover.

If lymphadenopathy is present on exam, consideration should be given to CT or ultrasound imaging, depending on location and other patient factors, such as risk for contrast induced injury, radiation exposure and others. The largest and most easily accessible node should be targeted for an excisional (surgical) or core biopsy (interventional radiology or surgical). Fine needle aspirates are inadequate for pathological confirmation of a lymphoproliferative disorder, necessitating a second biopsy and resulting in a delay in diagnosis and treatment. This should be sent specifically for "lymphoma protocol" or the local correlate, such that part of the tissue is saved fresh for flow cytometry testing. In the case of concern for hepatosplenomegaly, abdominal ultrasound can be performed. If concerns remain from initial workup, then referral to a hematology specialist should occur. **Figure 2** summarizes an initial approach to the work-up of suspected hematologic malignancy in the patient who presents with pruritus.

During the course of workup, providers may wish to treat the unpleasant symptom of pruritus. While first line therapy remains topical treatments (i.e., corticosteroids), emollients and anti-histamines, other therapies with varying efficacy for refractory pruritus can be considered. These include gabapentin, mirtazapine, and SSRIs. A systematic review of itch

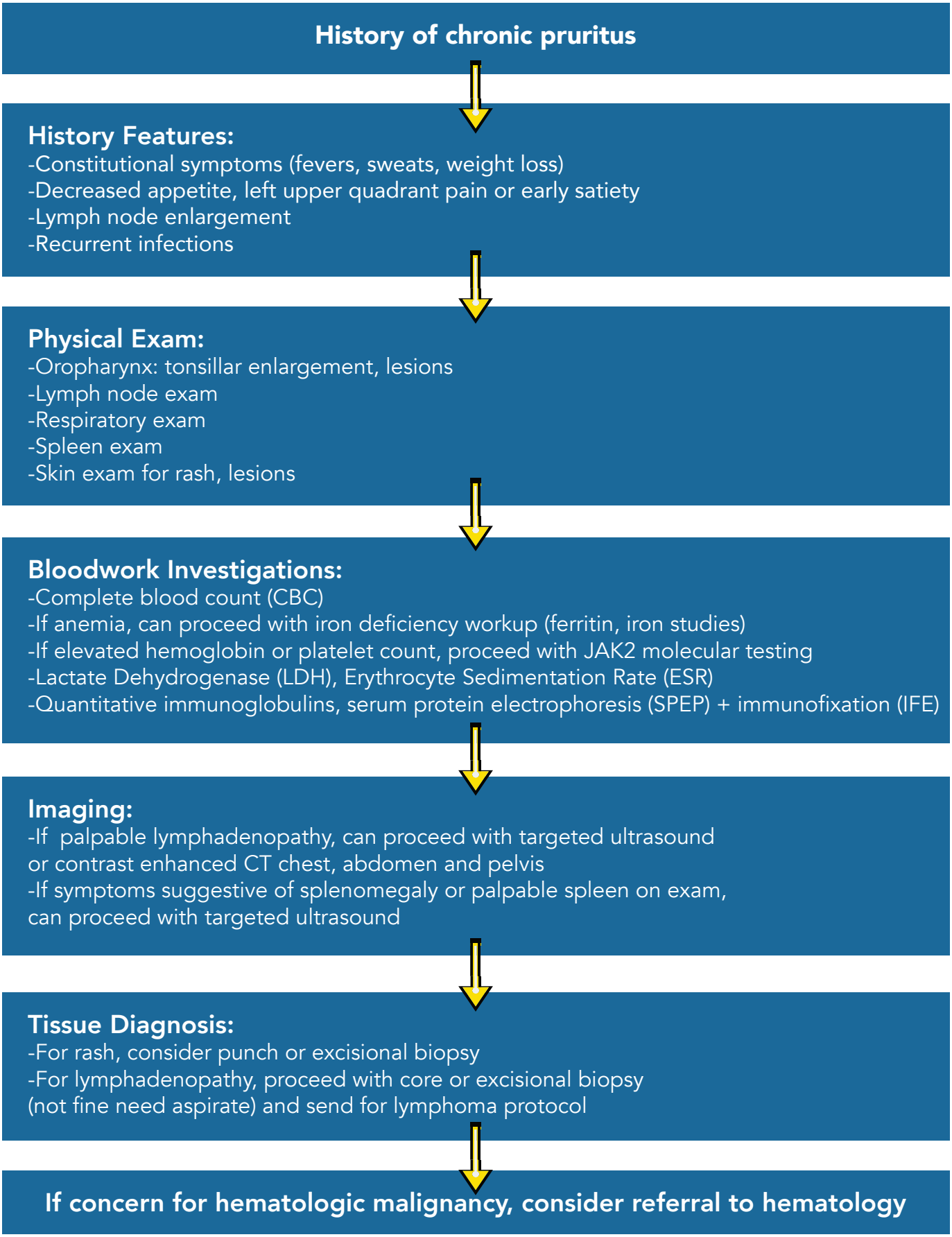

Figure 2. *Suspected hematologic malignancy work-up; courtesy of Amaris Balitsky, MD and Gwynivere Davies, MD*

in cutaneous T cell lymphoma demonstrated efficacy of the antiemetic aprepitant, specifically targeting substance P.[12] For all patients, the potential toxicity of treatment has to be weighed against the patient's discomfort. Definitive treatment of the underlying disorder once identified remains the mainstay of management.

Conclusion

Pruritus is a common symptom that all individuals have experienced at some time. Although general malignancy is a rare cause of pruritus, there is an increased risk of hematologic malignancy in those with chronic itch. For the allergist assessing chronic itch, we have outlined an approach in the case of suspected hematologic malignancy and steps for an initial work-up.

Patient data and photos obtained with consent.

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Financial Disclosures:
Amaris Balitsky reports honoraria from Novartis, BMS and Kite/Gilead
Gwynivere Davies reports honoraria from Roche and Janssen

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