Hardaway first described the presence of “multiple tumors of the skin accompanied by intense itching” in an otherwise healthy female patient in 1880. Similar firm, pruritic nodules distributed predominately over the extremities were discovered in three additional middle-aged women, and Hyde subsequently coined the term “prurigo nodularis” to describe these lesions. Today the pathogenesis of prurigo nodularis (PN; synonymous with “nodular prurigo”) remains unknown, though skin changes are thought to be secondary to mechanical trauma from scratching. Because PN lesions themselves are inherently pruritic, a vicious scratch-itch cycle forms that is difficult to break. Dome-shaped, papulonodules of one to three centimeters in size form, usually symmetrically, with typical distribution on the extensor surfaces of the extremities. Lesions may be present elsewhere on the body, but the upper, middle back, where the patient cannot easily reach, is typically spared. The resulting pattern of involved and clear skin is referred to as the “butterfly sign,” originally described by Reynolds.

Diagnosing PN can be challenging. While the disorder may be idiopathic, it has been associated with a variety of systemic or psychological conditions and is often characterized as eczema, although a true eczematous eruption may not be present at all. Nearly half of patients with the condition have been noted to have atop dermatitis (AD) or a predisposition to its development. Interestingly, lesions in patients with PN have been found to have extracellular deposition of eosinophil granule proteins out of proportion to the number of eosinophils. This histological finding is similarly present in skin affected with AD, suggesting that PN may be a nodular variant of the disease. Alternatively, the pruritus associated with AD may simply provide an impetus for lesion formation given that several pruritic, systemic conditions including liver dysfunction, kidney dysfunction, and hematologic malignancies have been shown to lead to PN. The robust association of these diseases with PN formation may warrant a complete blood count (CBC) and chemistry panel workup in select patients. Alternatively, further investigation into other potential systemic causes of PN, including HIV, infection, and thyroid disease may be considered when the association is in question.

Psychological conditions may also underlie PN pathogenesis due an intricate relationship between the psyche and pruritus. Individuals with delusions of parasitosis, a condition in which there is a false belief of parasitic infestation, have been noted to form PN. Similarly, patients with Morgellons disease, a disease that many regard as being on the same spectrum as delusions of parasitosis, can exhibit these lesions (See “Focus on Morgellons Disease on p. 63”). Regardless of the etiology of PN formation, it is important to acknowledge the psyche of affected patients, as the pruritus associated with these lesions can both aggravate and initiate psychiatric sequelae, which can further perpetuate lesion formation.

Mimickers
The diagnostic dilemma associated with PN can further be attributed to cutaneous mimickers. Pemphigoid nodularis, a rare form of bullous pemphigoid, imitates the lesions of PN. In order to differentiate between the two conditions, a biopsy with immunofluorescence should be performed as pemphigoid nodularis lesions contain serum complement 3 (C3)
and immunoglobulin (IgG) along the basement membrane. 

This diagnosis may not be straightforward, however, as there is evidence that PN lesions may precede pemphigoid nodularis development. Some hypothesize that scratching PN lesions may lead to antibody formation following disruption of the basement membrane, and previous case studies have reported cases of pemphigoid nodularis with evidence of positive immunofluorescence in lesions that previously had negative staining. 

Hypertrophic lichen planus is an additional condition that appears similarly to PN. Its typical location on the anterior aspect of the lower legs can further complicate diagnosis. While histology can at times differentiate these two lesion types, often the histologic findings are too similar. It has been suggested that dermoscopy may better discern these lesion types, as both exhibit specific patterns and several dermatoscopic findings are restricted to hypertrophic lichen planus including gray-blue globules, comma-like openings, and brownish black globules. 

Epidermolysis bullosa pruriginosa, a rare subtype of epidermolysis bullosa, should further be considered in the differential diagnosis of PN due to the presence of similar nodules. While this condition often presents with trauma-induced blisters, it is frequently misdiagnosed as PN, partially due to its typical location on the anterior aspect of the shins. 

Similar to PN, acquired perforating disorders can be attributed to systemic conditions, including diabetes and renal disease. Perforating disorders are characterized by the elimination of dermal connective tissue through the epidermis. The associated lesions can be differentiated from those of PN given the typical presence of umbilicated papules or nodules with a central keratotic plug. 

Differentiating the two conditions is not straightforward, however, and patients may have concomitant disease, given that systemic conditions may simultaneously induce perforation as well as pruritus, leading to the formation of PN. To further complicate the matter, some argue that these perforating disorders are simply an umbilicated variant of PN. In a study of 23 patients with chronic pruritus, lesions with eschar-like necrotic centers were histologically analyzed. These lesions were determined to have all histologic findings of classic PN in addition to breaks in the epidermal basement membrane, allowing collagen fibers to pass, a finding characteristic of perforating disorders. While the etiology of acquired perforating conditions is unknown, some hypothesize a mechanical cause. Mechanical disruption secondary to scratching may help explain the overlap of this condition with PN. 

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Alison D. Treister, BS, BSHS is a medical student at the Northwestern University Feinberg School of Medicine in Chicago.

Peter A. Lio, MD is a Clinical Assistant Professor of Dermatology and Pediatrics at Northwestern University Feinberg School of Medicine and a partner at Medical Dermatology Associates of Chicago.

FOCUS ON MORGELLONS DISEASE

Morgellons disease is characterized by patient belief in the presence of fibers or other inorganic objects within the skin, and PN lesions can form secondary to the skin manipulation associated with picking at these objects. It is important to note that the etiology of Morgellons is controversial, however, and some attribute the condition to borreliosis infection due to evidence of spirochetes described in one series. Others support a psychiatric cause of Morgellons, noting a lack of characteristic laboratory abnormalities and absence of common underlying medical conditions in affected patients. In 2012, the Centers for Disease Control and Prevention conducted a study on 115 patients affected with Morgellons and found that biopsied lesions had no evidence of parasitic, bacterial, or fungal infection. Furthermore, foreign material obtained from the skin was most often composed of cotton, and a majority of patients were determined to have co-morbid neuropsychiatric conditions.