Prurigo Nodularis

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Synonyms of Prurigo Nodularis

- prurigo nodularis of Hyde
- nodular prurigo
- Picker's nodules
- atypical nodular form of neurodermatitis circumscripta
- lichen corneus obtusus
- PN

General Discussion

Summary

Prurigo nodularis (PN) is a chronic inflammatory skin disease where an extremely itchy, symmetrically distributed rash appears most commonly on the arms, legs, the upper back and/or the abdomen. The itch associated with PN is so severe that it often interferes with sleep and psychological wellbeing. PN can appear on its own or be associated with other skin diseases or underlying medical conditions that affect multiple body systems, such as cancer, diabetes, chronic kidney disease or AIDS. The exact cause of PN is unknown, but altered function of the immune system and nerves in the skin is believed to be associated with heightened sensations of itchiness (pruritus) that leads to frequent scratching. Frequent scratching and picking of the skin is also thought to contribute to further lesion thickening and formation seen in the disease. PN can occur at any age but is more common in the elderly. When PN occurs in younger patients, it is more likely to be associated with inflammatory skin diseases, usually eczema (also called atopic dermatitis). Diagnosis is usually made by a dermatologist based on clinical symptoms and response to medications, but microscopic examination of a skin biopsy can aid in confirming the diagnosis. Although no FDA-approved treatments for PN currently exist, treatments used for other skin disorders ranging from topical creams to medications that alter the immune response are sometimes prescribed for patients with PN.

Signs & Symptoms

The rash associated with prurigo nodularis varies in appearance from patient to patient and is thought to occur from excessive, chronic scratching and picking due to sensations of intense itchiness (pruritus), burning and stinging. Pruritus associated with PN is usually severe; occurs in episodes but can be continuous; and is chronic, lasting longer than 6 weeks. It is typically worsened by sweat, heat, clothing, and stress.

The rash can range in severity from just a few to several hundred lesions and lesions can range in size from a half centimeter to 2 centimeters wide. Lesions are usually symmetrical in distribution and can appear as firm, dome-shaped papules, nodules or plaques. Papules, nodules and plaques vary by width and depth in the skin layers. A papule is less than 1 cm in diameter and elevated above the skin surface; nodules are greater than 1 cm in diameter, extend into the dermis (skin layer beneath the top layer of the skin, the epidermis) and can be above, below, or level with the skin surface; plaques are elevated lesions greater than 1 cm in diameter and are broader than they are deep.

Skin areas affected by PN become thickened (hyperkeratotic) as the protein keratin that makes up skin becomes overly abundant, similar to what happens with the formation of corns and calluses and dry and leathery (lichenified) as is seen in other skin conditions such as eczema where skin is repeatedly scratched. Lesions can be flesh-colored, pink, red, brown or black. Complications can occur if lesions become infected by bacteria. Healed lesions may leave scars and discolored marks.

Lesions are most commonly found on the back of the scalp, trunk of the body (abdomen and upper and lower back) and on the arms and legs. The central back is usually lesion-free, presumably because this area cannot be easily scratched to contribute to lesion formation.

Symptoms of PN require medical treatment and lesions rarely disappear spontaneously without treatment.

Causes

Although the exact cause of prurigo nodularis is not known, symptoms are thought to stem from dysregulation of the nerves and immune system in the skin.

Skin layers from top to bottom include the epidermis and dermis and both contain nerve fibers. Microscopic examination of skin biopsies in areas with and without lesions in PN patients has revealed a reduced number of nerve fibers in the epidermis but an increased number in the dermis. However, it is unknown if these changes in nerve fiber density are a cause or an effect of chronic scratching of the skin. With successful treatment of pruritus, skin nerve fiber density returns to normal. Another important finding in PN skin that distinguishes it from similar appearing skin diseases is an increase in structures important for skin sensation: Merkel cells, a special type of nerve cell, in the epidermis and papillary dermal nerves in the dermis.

Compared to healthy patients, the skin of PN patients also has more immune cells that produce chemicals called cytokines that are involved in inflammatory responses that may contribute to increased itchiness. These cytokines include interleukin-4, -13 and -31 and are targeted by some medications currently used and being developed to treat PN. Increased release of substance P; vanilloid receptor subtype 1; and calcitonin-related gene peptide, proteins from skin nerves, is also believed to contribute to the pruritus of PN. Other alterations to the skin environment include an increased number of neutrophils and mast cells that release histamine and increased activity from eosinophils. The latter two types of immune cells are best known for their involvement in allergic reactions and eczema.

Prurigo nodularis can occur on its own or can be associated with other skin diseases (dermatoses) or with infections, systemic diseases, neurological conditions or psychiatric conditions. The severity and outcome of PN are not predicted by the underlying cause.

PN is most often found in patients with other skin diseases that are typically pruritic, including atopic dermatitis (eczema), cutaneous T-cell lymphoma, lichen planus, xerosis cutis, keratoacanthomas and bullous pemphigoid.

Infections associated with PN include bacterial infections with tuberculosis, mucogenicum and H. pylori; viral infection with herpes zoster and hepatitis C; and parasitic infections with ascaris and strongyloidiasis.

Systemic diseases that PN can be associated with include: HIV; kidney disease; liver disease; thyroid disease; hyperparathyroidism; hyperpituitarism; diabetes; gout; iron deficiency anemia; celiac disease; polycythemia vera; amyloidosis; and certain cancers, especially blood precancers (myelodysplasia, MGUS) and blood cancers (leukemia, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma, multiple myeloma, primary cutaneous lymphoma), liver cancer, skin cancer, bladder cancer, lung cancer and cancers of the GI tract and female reproductive organs. Proper treatment of systemic and infectious causes may cure PN in some but not all cases.

Neurological causes of PN are related to damage to the brain and spinal cord (less typically) or to the area of the nervous system throughout the rest of the body outside of the brain and spinal cord (more typically). Neurological conditions associated with PN include nerve damage from herpes or shingles infections, polyneuropathies, brachioradial pruritus, notalgia paresthetica, small fiber neuropathies, sensitive skin and post-burn itch.

Psychiatric causes of PN include psychogenic pruritus. Psychogenic pruritus is an itching sensation associated with depression, anxiety, and dissociative disorders that lead to excessive scratching that can then lead to the skin changes associated with PN.

Some medications may also cause PN. These include the chemotherapy agents pembrolizumab, paclitaxel, and carboplatin. PN in these cases is thought to be from prolonged activation of the immune system post-treatment.

Affected Populations

The number of new cases of PN per year (incidence) in the US is estimated to be 72 per 100,000 people, or 87,634 people a year in people aged 18 to 64 years old. PN is more common in the elderly, and in women (54.2%) compared to men (45.5%), with women experiencing more severe pruritus. While PN can occur at any age, it is more likely to occur between ages 40 to 69 years old. Younger patients with PN are more likely to have other skin disorders associated with allergic states, such as eczema. PN is 3.4 times more common in African Americans. It is more prevalent among patients with HIV infection.

Related Disorders

PN is typically diagnosed based on clinical symptoms. Due to this and symptom overlap with other conditions that cause severe, chronic pruritus, PN can be mistaken for other skin diseases and can co-occur with some of them as well. These include:

Pemphigoid nodularis – a rare type of autoimmune disease and variant of the disease bullous pemphigoid where fluid-filled blisters form on the skin of the arms and legs, usually in the elderly. Unlike PN, pemphigoid nodularis may go away on its own after several months to years.

Actinic prurigo – a skin condition typically affecting girls where itchy papules and nodules appear after the skin has been exposed to the sun, usually on the upper extremities, face and neck. It typically begins in the spring and persists through the winter.

Epidermolysis bullosa – a genetic skin disorder that normally appears in childhood that is characterized clinically by blister formation from mechanical trauma or friction against the skin.

Lichen simplex chronicus (neurodermatitis) – a common type of eczema confined to one to two patches of skin that worsens with continued scratching.

Lichen amyloidosis – a subtype of primary localized cutaneous amyloidosis where papules appear on the shins and forearms as a result of abnormal protein deposits in the skin due to altered protein metabolism.

Hypertrophic lichen planus – a rare, chronic, inflammatory autoimmune skin and mucous membrane disease. Lichen planus (LP) most commonly presents as itchy, shiny, reddish-purple spots (lesions) on the skin (cutaneous LP) or as white-gray lesions in the mouth or on the lips (oral LP). Less commonly, LP may also involve the genitals (penile or vulvar LP), scalp (lichen planopilaris), ears (otic LP), nails, eyes and esophagus. Similar to lichen found growing on trees and rocks in forests, the skin lesions are often flat-topped and can be somewhat scaly, hence the name “lichen” planus. HLP in particular is the most common mimicker of PN.

Dermatillomania –a mental condition related to obsessive compulsive disorder (OCD) where lesions form after chronic skin-picking, and picking may occur up to several hours a day.

Nodular scabies – skin nodules that appear after infection with and treatment for the skin mite scabies. Nodular scabies is thought in some cases to be a persistent reaction to remaining mite parts in the skin. It consists of itchy nodules usually found in the groin and armpit and occurs in about 7% of scabies infections.

Lupus erythematosus – an autoimmune condition that can affect multiple organs and body systems including the skin. Some cases of lupus are isolated to the skin, most commonly discoid lupus erythematosus (DLE), and some rashes associated with lupus can resemble PN. These PN-resembling lupus rashes are distinct from the cardinal butterfly lupus-associated rash occurring outside of the face and characterized by thick and scaly patches that can itch.

Multiple keratoacanthomas – skin tumors from hair follicles that appear as nodules lined with blood vessels and a keratin plug. They may be associated with Muir-Torre syndrome, a rare inherited cancer syndrome where a rash of many of these skin growths occurs alongside an organ-specific cancer, usually colorectal cancer. Keratoacanthomas grow rapidly within days to weeks and cause scarring. They're usually found on sun-exposed skin.

Atopic dermatitis – the most common type of eczema that's chronic and caused by an overactive immune system that damages the skin barrier to cause dryness, itching, rashes and increased susceptibility to skin infections. It typically begins in childhood and is associated with other allergic conditions like asthma and hay fever.

Psoriasis vulgaris – an inflammatory, chronic skin condition and most common type of psoriasis characterized by red, raised skin plaques with white, shiny scales that can appear in multiple skin locations after localized skin trauma or irritation.

Diagnosis

For the best accuracy in diagnosis and to distinguish rashes of PN from similar skin disorders, clinical examination of signs and symptoms by a dermatologist combined with microscopic examination of lesions is recommended. Microscopic examinations include dermoscopy and biopsy, and these two methods combined together provide the best likelihood of an accurate diagnosis. With dermoscopy, dermatologists use a magnifying scope that shines light onto the skin to examine its structure through a portion of the dermis. It is a relatively new exam that was originally used to distinguish between different skin cancers but is now used to diagnose other skin disorders, including inflammatory and

infectious ones. It is non-invasive and therefore not painful or likely to cause infection. Biopsy, on the other hand, is simple procedure where portions of the skin are removed with a blade to allow dermatologists to see the skin in greater detail under a microscope.

Before microscopic examination, clinical clues alone that lead dermatologists to suspect PN include the distribution of the lesions on specific areas of the trunk and limbs; the physical characteristics of the rash, including darkened color, firmness, and itchiness; and the presence of other diseases that co-occur with PN in some cases.

Biopsy of PN lesions reveals thickening of different areas of the outermost layer of the skin (the epidermis) with distinct changes to the skin protein keratin (e.g. hyperkeratosis). The layer below the epidermis, the dermis, shows an increase in several inflammatory white blood cell types, including lymphocytes, mast cells, neutrophils and macrophages. A decreased number of nerve fibers in the epidermis and an increased number in the dermis are also characteristic findings. Appropriate treatment often causes nerve fiber density in both layers to return to normal.

Once PN diagnosis is confirmed from clinical and microscopy exams, blood tests including a complete blood cell count (CBC), a comprehensive metabolic panel (CMP) that included liver and kidney function tests, and thyroid hormone panel may be beneficial for diagnosing systemic diseases that may be contributing to the PN diagnosis, especially in patients who have PN without the more commonly associated skin conditions that can co-occur with it. Stool exams for the presence of parasites and HIV testing may also be beneficial when infectious causes of PN are suspected.

Standard Therapies

Standard treatments for PN are both behavioral and medical. No FDA-approved treatment currently exists for PN, but many medications used to treat other skin disorders or immune dysfunction are used to treat PN.

Behavioral treatments for PN include ways to prevent scratching and dryness, such as keeping fingernails short, wearing long sleeves and gloves, bandaging lesions, cleaning skin with gentle cleansers, keeping skin moisturized with non-irritating lotions and avoiding warm environments to reduce sweating. Recommended anti-itch lotions include calamine, menthol and camphor lotions.

Topical medications and medications injected directly into lesions (intralesional therapies) are also used for PN. Topical medications include corticosteroids, calcineurin inhibitors, capsaicin (the spicy ingredient in chili peppers) and vitamin D. Intralesional therapies include injected corticosteroids, such as injection with triamcinolone acetonide. The first types of treatment usually prescribed are antihistamines, topical corticosteroids and bandaging of lesions at night to prevent scratching.

If first-line treatments are not successful, treatments including cryotherapy, phototherapy, and medications that suppress the immune system (immunosuppressants) are used to control symptoms. Cryotherapy is considered an alternative treatment. It involves applying freezing or near-freezing temperatures to the skin to improve the appearance of lesions and relieve itching. Phototherapy uses UVA and/or UVB light to heal lesions faster and reduce pruritus and is suspected to work by decreasing levels of calcitonin-gene related peptide, substance P and histamine released by inflammatory cells. Immunosuppressants are reserved for the most resistant cases of PN because they affect more body systems and can have more serious side effects. Specific immunosuppressants prescribed for PN are cyclosporine, methotrexate, azathioprine, cyclophosphamide and tacrolimus. Intravenous immunoglobulin, while not an immunosuppressant but a treatment for immune-mediated diseases, has also been used in PN. It involves using antibodies from donors to modulate abnormal immune responses. General adverse effects of immunosuppressants include interference with kidney function (nephrotoxicity), liver inflammation, high blood pressure, high potassium levels (hyperkalemia), high uric acid levels (hyperuricemia) and GI symptoms.

Other treatments include antidepressants known as selective serotonin reuptake inhibitors (SSRIs); gabapentin, an antiseizure drug that also treats nerve pain; and sedatives, especially if sleeping difficulty from night-time itch occurs. These medications along with psychotherapy and relaxation therapy can help combat the psychological effects of PN as well.

Investigational Therapies

Newer treatments tried in PN patients include thalidomide, lenalidomide, opioid receptor antagonists, neurokinin-1 receptor antagonists and monoclonal antibody therapy.

Thalidomide depresses the nervous system by inhibiting inflammatory cells known as tumor necrosis factor-alpha (TNF-alpha) to treat the itch and inflammation seen in PN. It can cause fatigue, peripheral neuropathy, blood clots and birth defects if taken by pregnant women. Lenalidomide, another form of thalidomide, is less toxic to the nervous system.

Opioid receptor antagonists are medications that bind to opioid receptors on nerve cells that transmit pain signals and are effective at relieving itching. Examples include the medications naloxone and naltrexone.

Aprepitant and serlopitant, a class of drugs known as neurokinin-1 receptor antagonists are also useful in PN patients. They inhibit substance P activity to reduce symptoms. Adverse effects include GI and neurological symptoms in the first 2 weeks of use, and they are contraindicated in patients with liver disease.

Monoclonal antibodies are novel PN treatments with fewer side effects than typical immunosuppressant drugs. They work by targeting specific cells in the immune system to inhibit the underlying pathology that causes disease symptoms. The monoclonal antibody nemolizumab targets the receptor for the cytokine interleukin-31 (IL-31), a suspected contributor to itch in PN patients and the monoclonal antibody dupilumab targets IL-4 and 13. Dupilumab is FDA-approved to treat eczema, asthma and chronic inflammation of the nasal passages and sinuses (chronic rhinosinusitis). Both medications are given as injections and have been helpful in clearing lesions in PN patients who have not responded to other treatments.

The monoclonal antibody vixarelimab targets the receptor for cytokines IL-31 and oncostatin M (OSM) and is currently being studied in a clinical trial as a treatment for PN.

Information on current clinical trials is posted on the Internet at https://clinicaltrials.gov/ All studies receiving U.S. Government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Tollfree: (800) 411-1222
TTY: (866) 411-1010
Email:

Some current clinical trials also are posted on the following page on the NORD website: https://rarediseases.org/for-patients-and-families/information-resources/info-clinical-trials-and-research-studies/

For information about clinical trials sponsored by private sources, contact: http://www.centerwatch.com/

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