Cutaneous Manifestations of

s Manifestations of Hepatitis C

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Background: The hepatitis C virus (HCV) is an RNA virus. HCV is a major cause of both acute and chronic hepatitis. Persons become infected mainly through parenteral exposure to infected material by blood transfusions or injections with nonsterile needles. Persons who inject illegal drugs, people who snort cocaine with shared straws, and health care workers who are at risk for

needlestick and other exposures are at highest risk for HCV infection. Another major risk factor for HCV is high-risk sexual behavior. The incidence of acute HCV infection has sharply decreased in the United States during the past decade, but its prevalence remains high (approximately 2.7 million Americans) because chronic hepatitis C (CHC) infection develops in approximately 75% of patients acutely infected.

Most patients with acute and chronic infection are asymptomatic. Patients and their physicians detect no indications of the conditions for long periods; however, CHC infection and chronic active hepatitis are slowly progressive diseases and result in severe morbidity in 20-30% of infected persons. Astute observation and integration of findings of extrahepatic symptoms, signs, and disease are often the first clues to underlying HCV infection.

Cutaneous symptoms or findings relevant to HCV infection manifest in 20-40% of patients presenting to dermatologists and in a significant percentage (15-20%) of general patients. HCV is suggested and must appear in the differential diagnosis of these patients to avoid missing this important but occult factor in clinical disease in the appropriate setting.

Extrahepatic manifestations of hepatitis C virus are numerous (Sterling, 2006). The most prevalent and most closely linked with HCV is essential mixed cryoglobulins with dermatologic, neurologic, renal, and rheumatologic complications. A less definite relationship to HCV is observed with systemic vasculitis, porphyria cutanea tarda, and the sicca syndromes

Pathophysiology: CHC infection is associated with many extrahepatic manifestations in joints, muscles, neural and gastrointestinal tissues, and skin. In this article, the many dermatologic manifestations of HCV are classified according to diseases with proven or suspected etiology or causation.

Primary causation results from direct infection of HCV in the skin, lymphocytes, dendric antigen-presenting cells, and blood vessels. An example of this type of disorder is the recent finding of epidermal cells with HCV-RNA particles.

Secondary causation occurs when HCV infection manifests in the skin due to epiphenomena resulting from the disruption of immune responses. Leukocytoclastic vasculitis due to cryoglobulinemia is a good example of a specific skin manifestation resulting from the production of immunoglobulins, with rheumatoid characteristics causing an immune complex–mediated vasculitis.

Tertiary causation of dermatologic manifestations results when the disruption of another organ infected or affected by HCV causes skin manifestations that are nonspecific and typical of skin responses to that organ; these responses result from a wide range of causes, including flushing and other findings of thyroid hormone release in early HCV-linked autoimmune thyroiditis. Chronic active

hepatitis leading to fibrotic liver disease in CHC infection can also cause cutaneous vascular changes, such as spider nevus and palmar erythema. Arteriovenous hemangioma, a benign acquired cutaneous vascular lesion, has also been reported to be associated with chronic liver disease, including chronic active hepatitis associated with HCV infection.

Another category of dermatologic manifestations in HCV infections in a causative schema includes those diseases in which an association has been identified, but the details of causation have not yet been clarified. Porphyria cutanea tarda (PCT) is a good example of this type of HCV-related disease in which causation is unexplained but undeniable. In patients with PCT, 70% are HCV positive.

Neoplastic dermatologic manifestations are another category of extrahepatic findings.

Dermatologic manifestations are associated with treatments of HCV infection, especially interferon.

The last category is suspected associations of the disorder in a causative schema. HCV genomic analysis by means of arduous gene sequencing of many viruses has led to the division of HCV into genotypes based on homology. Arabic numerals denote the genotype, and a letter denotes the subtype for lesser homology within each genotype (Bonkofsky, 2001).

- Genotype 1a occurs in 50-60% of patients in the United States. This type is difficult to eradicate using current medications.
- Genotype 1b occurs in 15-20% of patients in the United States. Subtype 1b is difficult to eradicate using current medications. This type is most prevalent in Europe, Turkey, and Japan.
- Genotype 1c occurs in less than 1% of patients in the United States.
- Genotypes 2a, 2b, and 2c occur in 10-15% of patients in the United States. These subtypes are widely distributed and are most responsive to medication.
- Genotypes 3a and 3b occur in 4-6% of patients in the United States. These subtypes are most prevalent in India, Pakistan, Australia, and Scotland.
- Genotype 4 occurs in less than 5% of patients in the United States. It is most prevalent in the Middle East and Africa.
- Genotype 5 occurs in less than 5% of patients in the United States. It is most prevalent in South Africa.
- Genotype 6 occurs in less than 5% of patients in the United States. It is most prevalent in Hong Kong and Macao.

Frequency:

- **In the US:** The prevalence of HCV seropositivity in the United States was 3.9 million persons (Alter, 1999). In persons who were seropositive, 65% were aged 30-49 years, and 74% of patients demonstrating positive results were positive for HCV RNA, meaning active viral replication continued to occur. An estimated 2.7 million persons have CHC infection. Genotype 1a occurs in 57% of patients; genotype 1b occurs in 17%. From 1989-1993, the occurrence of HCV decreased 80%, from 50 cases per 100,000 to approximately 28,000 new cases per year. Decreased transfusion-associated disease and a dramatic decrease in intravenous drug use account for this change.

- **Internationally:** Worldwide, 170 million persons have HCV infection, which represents 3% of the world population (WHO, 1997). The prevalence of HCV antibody is less than 3% in developed nations. The prevalences are as high as 70% in highly endemic countries, such as Egypt; the high prevalences relate to specific practices that transmit the disease at specific times in the population.

Mortality/Morbidity:

- Although acute HCV infection is usually mild, chronic hepatitis results in at least 75% of patients (Bonkovsky, 2001). While liver enzyme levels may be in the reference range, the presence of persistent HCV-RNA levels discloses chronic infection. Biopsy samples of the liver also reveal chronic liver disease in patients. Cirrhosis develops in 20-50% of patients with CHC infection. Liver failure and hepatocellular carcinoma (HCC) can eventually result. HCC occurred in 11-19% of patients. The risk of cirrhosis and HCC doubles in patients who have undergone transfusion (Gordon, 1998).

- Two studies of compensated cirrhosis in the United States and Europe showed that decompensation occurred in 20% of patients and that HCC occurred in approximately 10% of patients (Hu, 1999; Fattovich, 1997). The survival rate at 5 and 10 years was 89% and 79%, respectively. The onset of CHC infection early in life often leads to less serious consequences (Seeff, 2000; Vogt, 1999). Hepatitis B virus (HBV) infection, iron overload, and alpha 1-antitrypsin deficiency may play a role in the progression of CHC infection to HCV-related cirrhosis (Obando, 1999; Banner, 1998).

- CHC infection and its major sequelae (cirrhosis and hepatoma) are responsible for 8,000-10,000 deaths a year.

Race: Race and ethnicity do not relate to HCV. HCV infection is associated with lower economic status, less education, and groups other than whites.

Sex: No sex preponderance occurs. Sex differences were not significant (Alter, 1999).

Age:

- Of individuals positive for antibodies, 65% are aged 30-49 years. Younger age at infection often relates to lesser consequences of the infection.
- Infection is uncommon in persons aged 20 years and younger and is more prevalent in persons older than 40 years (Nakashima, 1995; Osella, 1997).
- Data suggest the presence of age-related methods of infection, such as nonsterile medical procedures, including vaccination and parenteral drug treatment (Kiyosawa, 1994).

History: CHC infection occurs after the acute infection in 70% of patients with HCV, which represents a high rate of chronicity for a viral infection. The development of chronic infection is not matched by the development of symptoms. Patients with CHC infection often have no symptoms for long periods.

Symptoms often first develop as clinical findings of extrahepatic manifestations of HCV. In a large study of the extrahepatic manifestations of HCV, 74% of medical workers with HCV infection demonstrated extrahepatic manifestations (Cacoub, 1999). Arthralgias (23%), paraesthesias (17%), myalgias (15%), pruritus (15%), and sicca syndrome (11%) were the most commonly occurring extrahepatic manifestations.

Cryoglobulinemia was demonstrated in 50% of patients, and HCV is the most common cause of this condition. Vasculitis, arterial hypertension, purpura, lichen planus (LP), arthralgias, and low thyroxine levels were associated with titers positive for cryoglobulin. Biologic manifestations common to CHC infection include titers positive for serum cryoglobulins (40-56%), antinuclear antibody (ANA) (10%), low thyroxine (10%), and anti–smooth muscle antibody (7%). Risk factors for manifestations of extrahepatic CHC infection include advanced age, female sex, and liver fibrosis.

Symptoms and clinical findings are most common in the joints, muscle, and skin. Arthralgias occurred in 20% of patients, skin manifestations in 17%, sicca syndrome in 23%, and sensory neuropathy in 9% (Cacoub, 2000:47-56).

Thrombocytopenia occurs in approximately 10% of patients. One or more autoantibodies frequently occur in CHC infection; these autoantibodies include ANA (41%), rheumatoid factor (38%), anticardiolipin antibody (27%), antithyroid antibody (13%), and anti–smooth muscle antibody (9%). One autoantibody was present in 70% of sera.

Patients also present with symptoms that are less specific and are often unaccompanied by discrete dermatologic findings. Pruritus and urticaria are examples of less specific clues to underlying HCV infection in the appropriate setting (eg, posttransfusion, organ transplantation, surgery, intravenous drug use, injury of the nasal mucosa from snorting cocaine through shared straws).

Patients with ongoing pathology associated with CHC infection that eventually results in organ failure can present with symptoms and signs in the skin. Pruritus, dryness, palmar erythema, and yellowing of the eyes and skin are examples of less specific findings in patients with end-stage liver disease with cirrhosis; these findings provide clues that lead to further evaluation of the underlying causes.

Patients with the mucosa-associated lymphoma tumors (MALT) syndrome itself tend to have bowel symptoms.

- CHC may be associated with pruritus to the extent that some authorities believe that patients with unexplained pruritus should be investigated for HCV infection (Dervis, 2005).

- Dermatologic manifestations of HCV infection

    - Primary dermatologic disorders associated with CHC infection
        - Lichen planus: See Lichen Planus for a discussion of symptoms.
            - LP is a pruritic papulosquamous disorder involving the skin, scalp, nails, oral mucosa, and genitalia (Chuang, 1999; Nagao, 2000:277-282; Nagao, 2000:282-3; Parodi, 1996; Sanchez-Perez, 1996; Mignogna, 1998; Mignogna, 2000; Arrieta, 2000).
            - The lesions and pathology are often typical unlike many papulosquamous skin disorders, such as seborrhea, atopic dermatitis, and contact dermatitis; these skin disorders have scaling, erythema, and pruritus and are included in the differential diagnosis of LP but lack its pathologic and clinical specificity.

        - Intracellular HCV infection of epithelial cells is proven for LP (Arrieta, 2000).
        - Often, the papular lesions of LP suddenly appear on the volar acral surfaces of the wrists and arms and are pruritic.
        - Oral symptoms are less common, but painful erosions can occur in OLP.
        - Hair loss in lichen planopilaris, exquisite pruritus of markedly hypertrophic plaques on the lower legs in hypertrophic LP, and painful genital erosions can be presenting findings.
    - Acral necrolytic erythema (Khanna, 2000): The symptomatology of acral necrolytic erythema includes pruritus associated with recurrent, erythematous, papular eruptions with blisters and erosions on the dorsal aspects of the feet and ankles. Pain is common with variable-sized erosions. Chronic lesions are hyperkeratotic plaques with erosions and peripheral erythema preferring the acral parts of the legs. These lesions provide unusually specific markers for HCV infection.
    - Sialadenitis: Symptoms include dry eye and sicca syndrome due to chronic destruction of the major and minor salivary glands by capillaritis.
    - Mooren corneal ulceration: Serious corneal ulcerations are often linked to HCV infection. Cross-reactivity to the HCV envelope protein and a corneal antigen appears to be causative. Pain, lacrimation, and loss of sight result (Monroe, 1998).
    - Leukocytoclastic reactions (some): This tends to appear as an eruption of palpable purpura on the lower extremities. It may represent an HCV immune complex disease.

- Secondary dermatologic disorders of CHC resulting from perturbations of the immune system
    - Cryoglobulinemia: Leukocytoclastic vasculitis occurs with type II mixed cryoglobulinemia in the skin and mucous membranes. Leukocytoclastic vasculitis also occurs with necrotizing small vessel vasculitis of the skin, kidneys, joints, and eyes. Disorders of this type belong to a group termed mixed cryoglobulinemia syndrome. These disorders display palpable purpura of the legs (which is worse distally and inferiorly), livido reticularis, ulcerations, urticaria, symmetric polyarthritis, myalgias, cutis marmorata, and fatigue.
        - The symptomatology is pruritus, pain, or Raynaud phenomenon resulting from vasculitic sludging in the postcapillary venules of immunologic material.

        - In all cases of cryoglobulinemia, an inflammatory reaction occurs with an influx of polymorphonuclear cells. Variable vascular damage and occlusion results in worsening degrees of pathology and symptoms; such pathology includes livido vasculitis with perturbation of superficial and deep vascular reflexes and mottling blue changes of the skin (cutis marmorata); pruritus; painful ulcerations of significant size resulting from arteriolar occlusion; and through-and-through necrosis of epidermis, dermis, and fat. Significantly, HCV localized to the intravascular debris and recently to the vessel wall establishes specificity to these reactions. Perhaps the clinical variability of vasculitic reactions is related to the degree of specificity of the vasculitis.
        - Urticarial vasculitis with HCV infection presents with painful urticarial blanching plaques of the limbs and chest that fade to residual hyperpigmented areas (Hamid, 1998). The 2 cases presented lacked cryoglobulins. Complete disappearance of arthralgias and skin and liver disease occurred with clearance of HCV infection, suggesting that urticarial vasculitis may result from HCV immune complex disease.
    - Sialadenitis: Dry mouth without dry eyes is the most prominent symptom of sialadenitis associated with HCV infection. Sialadenitis is an inflammatory disorder of the salivary, parotid, sublingual, and minor glands. Findings include xerostomia resulting from a chronic lymphocytic infiltrate and destruction of the salivary glands. Sjögren disease and its markers ssRo and ssLa are not found (Haddad, 1992; Mignogna, 2000). As many as 15% of patients with CHC infections have sicca syndrome.
    - Mooren corneal ulcer: Serious corneal ulcerations begin at the rim or periphery and can progress singly or multiply and bilaterally to destroy the cornea. Symptoms of ulceration are eye pain, inflammation, tearing, and loss of vision due to corneal opacity and destruction.
    - Antiphospholipid syndrome is a serious multisystemic illness resulting from pathologic production of the antiphospholipids anticardiolipin and lupus anticoagulant. These IgG molecules (sometimes IgM or immunoglobulin A [IgA] in less severe variants) bind to platelets, vascular endothelium, beta-2 lipoproteins, prothrombin, and other phospholipids. The resultant pathologic processes depend on the locale of the process. Severe coagulopathies in the eye, the brain, the

kidney, and large vessels result in symptomatology referable to vascular destruction or bleeding in these organs.

- Tertiary dermatologic disorders (nonspecific disorders manifesting as a result of organ failure or disease of the skin associated with organ diseases). Symptoms are those of disease in the specific organs, as follows:
  - Liver failure in CHC infection results from cirrhosis, autoimmune hepatitis, cholangitis, and HCC. Symptoms of liver failure are identical to symptoms caused by other conditions, such as ascites, jaundice, and liver failure.
  - Thyroid failure: Thyroid destruction then failure occurs. Symptoms of hypothyroidism are noted.

- Dermatologic manifestations in which the exact pathogenesis is not further specified

  - Behçet syndrome: Symptoms form the major criteria for diagnosis of this disorder (see Behcet Disease). Findings for the major criteria include recurrent oral ulcerations appearing in young adults in their 20s and 30s with uveitis and genital ulcerations. Organs involved include the eyes, brain, lungs, GI tract, and kidneys. Aphthae and genital ulcerations are painful erosions. Uveitis causes pain, vision problems, and lacrimation, as well as other symptoms.
  - Canities: Graying of hair occurs with various conditions as well as naturally with aging.
  - Prurigo (prurigo nodularis): Prurigo nodularis appears as a heaped keratotic inflammatory nodule on the extensor surfaces of the arms, legs, and trunk. Lesions are pruritic, and patients find themselves incessantly picking them with their fingers and nails.
  - Lichen planus: See primary dermatologic disorders for symptoms of LP.
  - Sialadenitis: Symptoms are the same as those of sicca syndrome.
  - Thyroiditis: Symptoms are manifested according to the stage of autoimmune thyroiditis.
  - Vitiligo: Symptoms are the same as those discussed in Canities.
  - Polyarteritis nodosa (Domingo, 1990): PAN is a rare systemic vasculitis caused by necrotizing lesions in small- and medium-sized arteries of the skin, nerves, muscles, joints, kidneys, liver, and GI tract. More often associated with HBV infection, PAN results from aneurysmal dilatation, hemorrhage, or ulceration in the affected artery. In PAN, false-positive results for HCV are more common than true positive results for HCV. Protean manifestations result. Major systemic symptoms of fever, malaise, and prostration occur. Clinical manifestations result from organ involvement. Skin nodulation, ulceration, and palpable purpura are common.

Mononeuritis multiplex is a common presentation. Acute muscle and abdominal pain and hypertension often occur.

- Pruritus (Davis, 1998): Extrahepatic manifestations of HCV infection occur in 74% of patients (Cacoub, 1999). Pruritus is one of the most common symptoms, occurring in 15% of patients. A study of HCV infection with pruritus showed that nonspecific lesions were associated with pruritus in two thirds of patients. Urticaria occurred in 5 of 29 patients, with urticarial vasculitis occurring in 1 patient. Atopic dermatitis occurred in 2 of 29 patients with HCV infection. LP was present in 4 of 29 patients, and cryoglobulinemia was present in 10 of 29 patients. Most patients in this group had xerosis and keratosis pilaris that were easily alleviated with emollients. Prurigo nodularis is more common in patients with HCV and pruritus than in other patients.
- Urticaria (Reichel, 1990) and urticarial vasculitis (Hamid, 1998): A study of 79 patients with urticaria detected anti-HCV antibody in 24% and HCV RNA in 22%. Genotype 1b was present in 71% of patients; genotype 2a, in 24%; and genotype 2b, in 6%. In patients with HCV, urticaria tends to last longer than the typical few hours, is associated with worse liver status, and leaves a brown stain. Clinical findings of urticaria are identical to those of hives.
- Erythema nodosum (EN): A nonspecific association, EN has multiple causes considered in the differential diagnosis, including viral infections. EN appears as erythematous, tender, dome-shaped elevations on the skin on the lower legs. EN lesions can be single or multiple, and they can demonstrate a reaction pattern on the skin resulting from panniculitic inflammation generated by various pathologic sources (eg, infections with bacteria, mycobacteria, Protozoa, fungi, viruses).
- Erythema multiforme (EM) (Neri, 1998): Bull's-eye lesions characterize this skin reaction pattern. EM can be asymptomatic, pruritic, or burning. As an immune response to adverse antigenic stimuli from endogenous or exogenous sources, the response can be limited to a few, many, or widespread urticarial lesions with surrounding erythema and central deeply erythematous spots. Overwhelming reactions of this type include oral and anal ulcerations, systemic symptoms, and prostration; this condition is termed Stevens-Johnson syndrome. HCV infection is just one of many possible causes of EM.
- Autoimmune thrombocytopenia: Symptoms of low platelet counts occur with petechiae and purpura. Ecchymosis occurs without symptoms. Bland petechial and ecchymotic hemorrhage must be included in the differential diagnosis.
- Leukocytoclastic vasculitis: This condition occurs as a result of circulating immune complexed depositing with endothelial cell gaps

in the skin and mucous membranes. The antigen is usually not known or determined, although it may be HCV.

- Dermatologic manifestations of CHC infection in which the cause is unknown are multiple.
    - PCT develops in patients who have 1 or more of the risk factors for PCT; the risk factors include exposure to chemical or toxic agents or drugs, iron overload, or excessive alcohol intake (Bulaj, 2000; Cribier, 1995).
        - PCT is manifested by blisters, vesicles, and milia on the acral dorsal surfaces of the extremities, especially the tops of the hands.
        - Hypertrichosis of the temples, pigmentary changes, scarring, sclerodermatous changes, chloracne, ulcerations, and dystrophic calcifications are commonly the result of skin fragility with symptoms of epidermolysis bullosa.
        - Uroporphyrins and hepatocarboxyl porphyrins collect in the skin, bones, and teeth after they spill into the blood once the liver is saturated. These pigments, found in the plasma, fluoresce and turn the urine dark red from renal excretion. Mild elevations in the levels of these substances and in urinary aminolevulinic acid (ALA) also occur, but porphobilinogen (PPG) levels are in the reference range.
        - Variegate porphyria and hereditary coproporphyria have the same clinical presentation, but PPG levels are elevated in these conditions.
        - The prevalence of PCT is related to the relative prevalence of HCV and major hemochromatosis and other iron overload genetic abnormalities.
        - In southern Europe where HCV is prevalent, 70-90% of patients with PCT have positive results for HCV.
        - Patients with familial PCT had negative results for HCV in one study. All patients with PCT with HCV had active multiplication of HCV.
        - In northern Europe, Australia, and England where the prevalence of HCV is lower, 20% of patients with PCT have detectable levels of HCV. In these countries, PCT is more closely related to the higher prevalence of the hemochromatosis gene abnormality.
        - In the United States, the prevalence of HCV in patients with PCT is intermediate at 56%.

- Dermatologic manifestations of malignancies associated with CHC disease

- Non-Hodgkin B-cell lymphoma (NHLB): A high prevalence (20-40%) of HCV antibodies occurs in NHLB, and the antibodies are not present in other lymphomas or hematologic malignancies (Luppi, 1998). Lymphomas producing cryoglobulins and low-grade mucosa-associated lymphoma tumors (ie, MALT syndrome) of the GI tract are associated with dermatologic manifestations. Antigen-driven B-cell proliferation from chronic stimulation is the proposed mechanism (De Re, *Blood,* 2000; Domingo, 1999; Wang, 1999; Guastafierro, 2000; Chang, 1999). NHLB presents like other lymphomas, with lymphoidal masses, gut associated masses, and symptoms of cryoglobulinemia with palpable purpura and ulcers of the lower legs.
- MALT syndrome: A study concerning the association of HCV and NHLB showed a prevalence of HCV of 37% (Vallisa, 1999). Patients were older, and more patients were female than male. A closer association to immunocytoma than to MALT syndrome was found. In 20 patients with immunocytoma, 13 had HCV infection, and localization to the orbit and mucosal surfaces was more common. HCV localized to a parotid lymphoma associated with a mixed cryoglobulinemia showed viral proliferation in parotid epithelial cells and not in NHLB cells (De Vita, 1995). Epstein-Barr virus and herpesvirus type 6 are the other sialotropic viruses not present in the reported cases. Local carcinogenic functions of HCV, effect on the p53 system, immunoregulation perturbations, and malignant transformation were considered in the etiology of the conditions.
- Hepatoma: The progression of HCV infection to CHC infection and then to HCC is a well-known sequence. The chronicity of HCV infection occurs in 60% of patients infected by the virus overall, but the rate increases to more than 90% in type 1b infection (Bonkovsky, 2001). Worse hepatocellular disease also resulted from type 1b infections. Hepatic cirrhosis is correlated with inoculation size, being more common in patients with HCV-infected blood transfusions (23%) and organ transplantation than in users of intravenous drugs (9%). Viral species variation, complications, and host antibody response vigor have a role in chronic infection (Villano, 1999). Cirrhosis develops in approximately 15-20% of patients with CHC. HCC eventually occurs in 5-10% of patients with CHC. Symptoms of hepatoma include rapid decompensation of the liver and metastases, often to the brain.
- Squamous cell carcinoma of the tongue: This condition is a rarely coexistent disorder, usually evident as an erosion on the tongue.

- Dermatologic manifestations associated with interferon alfa therapy for HCV infection

- Erosive OLP and epidermolytic hyperkeratosis may occur with interferon alfa therapy for CHC infection (Schlesinger, 1997).
- Capillaritis may be present with interferon alfa treatment of CHC infection (Gupta, 2000).
- Lichen myxedematosus may worsen during interferon alfa-2a therapy for chronic active hepatitis.
- Thyroiditis may occur during interferon therapy.

- Possible conditions associated with HCV infection

  - Erythema dyschromicum perstans is an asymptomatic condition of ashy gray discoloration of the skin on the extensor surfaces of the arms and face.
  - Porokeratosis, the disseminated superficial type, is associated with HCV infection or HCC. Eruptive disseminated porokeratosis in relation to the onset of HCC occurred in 3 closely observed patients with CHC infection and persistent HCV hepatitis. Both conditions are believed to be related to immunomodulation of the *p53* gene. HCV core protein may affect cancer transformation directly through an effect on a promoter gene expression (Kono, 2000). The core protein is a multifunctional protein with the capacity to bind to the so-called death domain of tumor necrosis factor receptor 1 (TNFR1) and the intracellular portion of lymphotoxin-beta receptor. The portion of TNFR1 active in apoptosis and antiapoptosis signaling pathway is the death domain affected by HCV (Tai, 2000).
  - Generalized granuloma annulare, an asymptomatic condition with dermal nodule formation resulting from an inflammation of collagen, may be present (Granel, 2002).
  - Symmetric polyarthritis and livido reticularis may occur (Shearer, 1997).
  - Asymptomatic, solitary, dome-shaped reddish papules, 5-10 mm in diameter, may be present on the face in some patients with HCV infection; these papules represent arteriovenous hemangiomas, which are seen with increased frequency in these patients.
  - Progressive pigmented purpura (Gougerot-Blum disease) is demonstrated as lesions of capillaritis on the lower legs with fine petechiae in various distributions (Chima, 2000).

Physical: Physical findings of extrahepatic dermatologic conditions associated with HCV infection have largely been presented in History. Physical findings of the disorders and diseases are clarified below.

- Primary dermatologic disorders of CHC in which HCV infection of the skin is proven or suggested

- LP presents as flat-topped pruritic papules or coalescent plaques on the extensor surfaces of the limbs and trunk. Some individual lesions may have a purple-red hue, a fine retiform surface scale (termed Wickham striae), and an angular appearance. Involvement of the scalp hair is a cause of alopecia of the scarring variety (termed lichen planopilaris). The leaf-shaped alopecic areas appear like fingertips touching the scalp with normal intervening areas. Oral involvement with buccal lesions is common. Gum, lip, and tongue involvement can be a chronic premalignant disorder. Lesions lack the specificity of skin lesions and present as purple-red mucosal patches. Occasionally, prurigolike nodules with heaped keratotic material on a thickened base occur on the limbs and trunk. Lesions on the genitalia can be nonspecific and are one cause of vulvar pruritus.

- The lesions of acral necrolytic erythema are flaccid bullae and described as large, painful, partially eroded, violaceous patches on the proximal half of the dorsal aspect of the feet extending over the medial and lateral malleolus (Khanna, 2000).

- Some leukocytoclastic reactions may occur.
    - Palpable purpura is the classic presentation of mixed cryoglobulinemia as leukocytoclastic inflammatory reactions in the skin.
    - Type III cryoglobulinemia results when no specific antigenicity of the immune reactants is identifiable. In this case, HCV may serve as one of the antigens. In CHC infection, 50% of patients have identifiable cryoglobulin levels.
    - Type II cryoglobulinemia was present in two thirds of patients with IgM RhF. Clinicians can identify the lesions by their purpuric and elevated nature and red or purple spots on the lower legs. Specific identification is by skin biopsy. The lesions result in ulcerations of various sizes and depths because the small venules and arterioles are obstructed, damaged, or ruptured by the inflammation generated by sludging of viscous immune reactants. Polyfunctional rheumatoid factor, usually IgM, attaches to available IgG molecules, forming enormous molecules that congeal and clog small vessels and vasa vasorum of the skin and joints. Associated neutrophilic inflammatory infiltrate leads to vascular injury and ulcerations of the lower leg, which are often exquisitely painful.

    - Sialadenitis associated with HCV infection can present as a sicca syndrome with dry eyes and mouth and ulcerations from destruction of the salivary and meibomian glands.

- Secondary dermatologic disorders of CHC infection (mostly as a result of perturbations of the immune system)

    - Cryoglobulinemia with leukocytoclastic and necrotizing small vessel vasculitis of the skin, kidneys, joints, and eyes. Physical findings in the skin include palpable purpura and ulcerations on the lower legs.
    - Sialadenitis presents as dry eyes and dry oral and nasal mucosa. Ulcerations occur late in the evolution of this disorder.
    - In Mooren corneal ulcer, corneal ulcers form on one or both eyes beginning at the periphery or limbus.
    - Antiphospholipid syndrome results in protean physical findings in the brain, kidneys, eyes, skin, joints, and major vessels because of thrombus formation and bleeding in these major organs.
    - Autoimmune, not further categorized
        - Behçet disease is described as presenting with oral, eye, and genital ulcerations that result from an unknown vasculitic process.
        - Canities may occur. Stories abound of people's hair suddenly turning white. CHC infection is one of the causes of the sudden disruption of the melanizing function of follicles.
        - Prurigo nodularis clinically appears as heaped keratotic masses on a thickened inflammatory base. Relentless scratching eventually causes excoriated masses in areas that the patient can easily reach; such areas include the shoulders, arms, upper part of the trunk, thighs, and anterior parts of the lower legs.
        - See Lichen planus for a discussion of the condition.
        - Scarring alopecia and sclerodermatous changes may occur on the hands, back, and chest (Jackson, 1998). A patient presented with erosions and blisters on the hands and back and sclerodermoid thickening and scarring of this skin in the setting of PCT.
        - Immune thyroiditis is the most common extrahepatic manifestation of CHC infection. Findings depend on the state of the thyroid destructive process. Findings of a diffusely enlarged gland and hyperthyroidism are noted early. A normal size and a granular feel as well as normal function are noted at one point, and, later, hypothyroidism with a shrunken gland is found because much of the thyroid is destroyed.
        - In thrombocytopenia, low platelet counts result in the spontaneous asymptomatic appearance of flat areas of

petechiae, purpura, and ecchymosis of the skin. Dependent areas are often involved first. Easy bruising is noted.
        - In vitiligo, areas of complete loss of pigmentation occur, and white spots develop on the skin.
        - Symmetric polyarthritis with livido reticularis is noted (Shearer, 1997).
        - Generalized granuloma annulare with HCV infection disappears with appropriate treatment of CHC infection (Granel, 2002).

- Tertiary dermatologic disorders (nonspecific disorders manifested because of organ failure or because disease is manifested in the skin)

    - Physical findings of liver failure result from cirrhosis, autoimmune hepatitis, cholangitis, and HCC. Findings include ascites, jaundice, upper GI tract bleeding, and various accompaniments of chronic and acute liver decompensation.
    - Physical findings of hypothyroidism include coarsened and thickened dry hair and skin and myxedematous plaques on the shins (see Hypothyroidism).

- Dermatologic manifestations of HCV infection in which the cause is uncertain but the association is certain: PCT is manifested by blisters, vesicles, and milia on the acral dorsal surfaces of the extremities, especially the tops of the hands. Often, hypertrichosis of the temples, pigmentary changes, scarring, sclerodermatous changes, and chloracne are present, and ulcerations with dystrophic calcifications result from skin fragility.
- Dermatologic manifestations of malignancies associated with CHC disease

    - Like all lymphomas, NHL appears as nodal masses with physical signs referable to the area where they develop and disrupt.
    - Clinical findings of verrucous squamous cell carcinoma of the tongue include a thickened patch in OLP on the tongue (Carrozzo, 1997). A possible relationship exists to altered *p53* gene transformation in squamous cell carcinoma and hepatoma in cirrhosis.
    - MALT syndrome appears as mass lesions in the orbit or in a gut-associated area (eg, salivary gland or intra-abdominal, hepatic, or other area).
    - Hepatoma physically appears as a mass lesion in the liver; a metastatic lesion, often to the brain or lung; and metabolic disruptions of those organs.

- Dermatologic manifestations of treatments for HCV infection

- Lichen myxedematosus may worsen during interferon alfa-2a therapy for chronic active hepatitis (Rongioletti, 1998). Asymptomatic, 2- to 4-mm, flesh-colored papules on the upper and lower extensor surfaces of the arms are noted. Lichen myxedematosus papules contain depositions of mucin in patients without thyroid disease who often have paraproteinemias. A localized form affects the head and neck, upper limbs, lower limbs, or trunk. A generalized form is termed scleromyxedema and affects large areas with sclerosis.
- Capillaritis is associated with interferon alfa treatment of HCV infection (Gupta, 2000). Pigmented purpuric eruptions on the lower legs consist of fine petechiae that appear after beginning treatment.
- Erosive OLP and epidermolytic hyperkeratosis may occur during interferon alfa-2b therapy for CHC infection. These conditions appear with erythematous, scaly plaques on the scalp, chest, back, buttocks, legs, and genitalia and painful ulcerations in the mouth. The skin lesions are psoriasiform with a reddened base and variable heaped-up scale. Wickham striae occur on the lips and intraorally (Schlesinger, 1997).

- Possible associations

  - Some patients with HCV infection have an asymptomatic, solitary, 5- to 10-mm diameter, dome-shaped reddish papule on the face, which represents arteriovenous hemangioma and occurs with increased frequency.

  - Gougerot-Blum disease is a manifestation of HCV infection (Chima, 2000). Lesions of capillaritis on the lower legs are noted with fine petechiae in various distributions.

Causes: The causes of extrahepatic dermatologic manifestations of HCV infection relate to the nature of the virus, the method of infection, host responses to HCV infection, and myriad feedback considerations. HCV is a flavivirus with a positive sense single-strand RNA (ssRNA); the ends of the RNA are conserved. HCV RNA encodes 3300 amino acids. The polyprotein encoded is cleaved by host and viral proteases to yield at least 9 polypeptide proteins, core peptides, and viral envelope proteins E1 and E2 (which encode for glycoprotein spikes set in the host cell membrane derived envelope).

Six nonstructural (NS) proteins, termed NS2, NS3, NS4a, NS4b, NS5a, and NS5b, include RNA polymerase, cyclase, and other proteins necessary for viral replication. Hypervariable regions of the E2 envelope protein are responsible for quasi-species generation. Some nonessential sequences of NS genes also create variability in antigenic structure. Mutation of NS3 sections results in escape mutants that conserve essential viral functions while interfering with host

T-cell function by down-regulating interleukin 2 and interferon gamma function and up-regulating interleukin 10 (Wang, 1999).

The chronicity of infection also relates to inoculum size, with high rates and worse disease in patients

who have undergone transfusions and organ transplantation. The resulting persistent infection and immune stimulation create the many immunologic epiphenomenon, such as LP, mixed cryoglobulinemia, and thyroiditis. A generation of factors unfavorable to apoptosis control functions may favor malignant transformation in CHC infection.

- Primary dermatologic disorders of CHC infection

    - Lichen planus: HCV particles are found in immune lymphocytes, macrophages, and dendritic cells, as well as in epithelial cells and cells of blood vessels (Ferri, 1995; Sansonno, 1995; Arrieta, 2000).
        - In LP, HCV replicates in OLP epithelial cells of lesional and nonlesional skin cells. What role this plays in developing the LP host response is not known. HCV perturbs the class II host response by impairing the ability of the dendritic or antigen-presenting cell to stimulate a good T-cell response (Kanto, 1999).
        - Lower expression of interferon gamma and interleukin 12 causes a blunted T-cell response to allostimulatory non–self-related new antigen. Another mechanism of class II immune response inhibition results from the hypervariable region (HVR-1) of envelope protein E2 suppressing $CD4^+$ lymphocytes, which are stimulated to respond to HCV. The HVR-1 acts as a T-cell receptor antagonist (Frasca, 1999).
        - A theory of causation, termed the superantigen theory of immune stimulation (which includes LP and many other immune-related disorders in which exact causation is a mystery), suggests that the human leukocyte antigen (HLA) class II response was disturbed. Superantigens, such as bacterial proteins and toxins, were proposed to act outside the HLA binding site to broadly stimulate an immune nonspecific response of wide varieties of T cells, including antiself immune responses.

    - Some leukocytoclastic reactions: Type II cryoglobulinemias in which IgM is the macromolecular rheumatoid antibody are more common than type III cryoglobulinemias. IgG was directed toward NS proteins and structural proteins. IgM antigen was the core protein, suggesting cross-reactivity to IgG (Hartmann, 1995). Co-

affinity of IgM anticore antibody to IgG may be a mechanism in the formation of the cryoprecipitate.

- Sialadenitis: This condition is a capillaritis of the accessory and main salivary glands and the eyes.

Secondary dermatologic disorders of CHC infection (mostly as a result of perturbations of the immune system).

- Cryoglobulinemia: Leukocytoclastic vasculitis of the skin, kidneys, joints, and eyes is present. Immune stimulation of T-cell clones in HCV infection produces monoclonal macroglobulins with co-affinity to a constituent of HCV and IgG. Stimulation of this rheumatoid factor is driven by anti-HCV activity sustained by the ongoing mutation of the virus. The same pathogenesis is involved for NHL associated with HCV.
  - The mean cryoprecipitate result was 2% in one study (Hartmann, 1995) but can be greater. Immunoglobulin M (IgM) directed to a core protein sequence of HCV was also directed to a homologous immunoglobulin G (IgG) heavy-chain amino acid sequence. IgG was directed to structural and nonstructural components of HCV. The material is usually monomeric IgM molecules with high affinity for IgG (also termed rheumatoid IgM molecules or RhF).
  - Type I cryoglobulinemias are caused by macroglobulins, such as in Waldenström macroglobulinemia, or IgG in which sludging results from massive molecules congealing in cooled venules of the lower leg.
  - Type II mixed cryoglobulins have a monoclonal rheumatoid species but vary in the IgG antigen, which is nonspecific.
  - Type III mixed cryoglobulinemias result from specific reactions of immunoglobulins to a single or well-defined antigen or various antigens, but the antibody species and the antigen are not monoclonal.

- Sialadenitis: This condition can result from acute bacterial or viral infection or autoimmune disease, as in Sjögren disease.

- Mooren corneal ulcer: Cross-reactivity to HCV envelope protein and a corneal antigen appears to be causative. A HCV envelope protein shares the antigenic specificity of this protein, resulting in Mooren ulcer in HCV infection. Other common etiologic causes may occur.

- Antiphospholipid syndrome: Immune reactant immunoglobulins with antiphospholipid activity are present.

- Autoimmune, not further categorized

    - Behçet disease: Behçet syndrome is believed to result from an unknown immunologic cause and results in a vasculitis that can cause coagulation and destruction of arteries and veins.
    - Canities: Illness and disease can affect melanogenesis of the hair.
    - Prurigo nodularis: A report of HCV infection with prurigo nodularis has been published (Neri, 1998).
    - Lichen planus: Lichen planus is most likely an immunologically mediated reaction.
    - Sialadenitis: This condition may result from an HCV infection in the salivary gland epithelium and may be a primary disorder of the glands.
    - Thyroiditis: Destructive inflammation results in early hyperthyroidism. As more of the gland is destroyed, thyroid function normalizes and then becomes subnormal in a hypothyroid picture.
    - Thrombocytopenia: Thrombocytopenia may be due to a number of causes. These include disorders producing diminished platelet production, altered platelet distribution, and increased platelet destruction. For example, an acute viral infection may produce an acquired defect in diminished platelet production. Medications may give increased platelet destruction. Low platelet counts result in the spontaneous asymptomatic appearance of flat areas of petechiae, purpura, and ecchymosis of the skin.
    - Vitiligo: A case of hair turning white as a result of HCV infection was reported.

- Tertiary dermatologic disorders (nonspecific disorders manifesting because of organ failure or because disease manifests in the skin): Persistent viral particles, persistent HCV hepatitis, and transformation are promoted by means already stated.

- Dermatologic manifestations of HCV infection in which the cause is uncertain but the association is certain: Proposed etiologic mechanisms for the relationship of CHC infection and PCT include oxidative stress from CHC and other viral infections (HBV and HIV) of hepatocytes that affect uroporphyrin decarboxylase (UDC) function. HIV infection causes increased serum porphyrin levels (Lim, 1998). Patients with hereditary PCT and patients with hemochromatosis have sufficient UDC redundant function to prevent the appearance of symptoms. Cytochrome P4501A2, metabolically active iron, CHC, long-term alcohol intake, and estrogens affect the rate of conversion of uroporphyrinogen to uroporphyrin by oxidation in hepatocytes. An increase in delta5-ALA synthetase activity can present excess uroporphyrin to the hepatocyte.

- The clinical and immunologic pattern of expression of Sjögren syndrome associated with chronic HCV infection was analyzed (Ramos-Casals, 2005). HCV-associated Sjögren syndrome is indistinguishable from the primary form in most cases. Chronic HCV infection was suggested as an exclusion criterion for the classification of primary Sjögren syndrome because the virus may be implicated in the development of Sjögren syndrome in a specific subset of patients. The phrase "Sjögren syndrome secondary to HCV" was recommended.

- Dermatologic manifestations of malignancies associated with CHC disease

  - Non-Hodgkin lymphoma: A protein amino acid sequence of HCV core protein has homology to a heavy-chain IgG sequence. The viral recognition reaction producing macroglobulin rheumatoid species antibodies may drive the mixed cryoglobulinemia reaction, and it may also cause lymphomagenesis.

  - Verrucous cell carcinoma of the tongue and OLP with HCV infection and replication: A possible relationship to altered *p53* gene transformation exists with squamous cell carcinoma and hepatoma in cirrhosis.

  - MALT syndrome: A study concerning the association of HCV and NHLB showed a prevalence of HCV of 37% (Vallisa, 1999). Patients were older, and more patients were female than male. A closer association to immunocytoma was found than to MALT syndrome. Thirteen of 20 cases of immunocytoma had HCV infection, and localization to the orbit and mucosal surfaces was more common. HCV localized to a parotid lymphoma associated with a mixed cryoglobulinemia showed viral proliferation in parotid epithelial cells and not in NHLB cells (De Vita, 1995). Epstein-Barr virus and herpesvirus type 5 are the other sialotropic viruses not present in the reported cases. Local carcinogenic functions of HCV, effect on the p53 system, immunoregulation, perturbations, and malignant transformation were considered in the etiology of the conditions.

  - Hepatoma: The ends of HCV RNA are conserved. HCV core protein is a multifunctional protein with a role in apoptosis-antiapoptosis regulation of cell multiplication and tumor control (Tai, 2000). The death domain of tumor necrosis factor 1 and the cytoplasmic tail of lymphotoxin beta bind to the core protein. Nuclear factor kappa B (NF-kB) is activated in core peptide-transfected hepatoma cells and in HCV-infected liver tissue. NF-kB

activation causes resistance to apoptotic signals in transfected HCV-containing cells. An evasion mechanism of host surveillance by means of NF-kB activation is proposed as one method of viral persistence in the CHC state and in carcinogenesis.

- Dermatologic manifestations of treatments for HCV infection: Interferon therapy increases the incidence of immune epiphenomenon and autoimmune disorders.

\Behcet Disease
Epidermolytic Hyperkeratosis (Bullous Congenital Ichthyosiform Erythroderma)
Erythema Dyschromicum Perstans
Granuloma Annulare
Henoch-Schönlein Purpura (Anaphylactoid Purpura)
Hypersensitivity Vasculitis (Leukocytoclastic Vasculitis)
Lichen Myxedematosus
Lichen Planus
Oral Lichen Planus
Pigmented Purpuric Dermatitis
Porokeratosis
Porphyria Cutanea Tarda
Prurigo Nodularis
Sjogren Syndrome
Sjogren-Larsson Syndrome
Urticaria, Acute
Urticaria, Chronic
Urticarial Vasculitis
Verrucous Carcinoma
Vitiligo

Other Problems to be Considered:

Acral necrolytic erythema
Sialadenitis
Mooren corneal ulcer
Antiphospholipid syndrome
Canities
Prurigo nodularis
Thyroiditis
Thrombocytopenia
Polyarteritis nodosa
Pruritus
Dermatologic manifestations of liver failure
Dermatologic manifestations of thyroid destruction and failure
Non-Hodgkin lymphoma

Mucosa-associated lymphoid tumor (MALT) syndrome
Hepatoma
Dermatologic manifestations of interferon alfa therapy
Livido reticularis
Symmetric polyarthritis
Arteriovenous hemangioma

Medical Care: Treatment of patients with extrahepatic dermatologic manifestations of HCV infection is the same as that of HCV infective state and the customary treatments of the individual conditions. Many, if not all, of the dermatologic manifestations disappear when appropriate HCV treatment or viral clearance occurs. Malignant conditions may even disappear with effective therapy for the underlying CHC infection.

- Currently, medical treatment of patients with HCV infection consists of interferon and ribavirin therapy.

- Medical therapy for patients with individual extrahepatic dermatologic manifestations of HCV infection depends on the condition.

Consultations:

- Involving specialists for both treatment and follow-up care often maximizes the care of individuals with extrahepatic cutaneous manifestations of HCV. Monitoring of liver status and liver disease progression is beyond the usual purview of dermatologists. Many physicians consult gastroenterologists and hepatic specialists in the care of patients.

- Cutaneous manifestations, serious vasculitis, lymphomas, hepatomas, and metabolic disorders may require high-level management with a team approach. Individual specialists may be an important resource in the care of patients.

Further Outpatient Care:

- Treatment of various primary, secondary, tertiary, HCV-related, and associated conditions is for the individual conditions. The continued successful care of patients requires attention to the underlying HCV infection of the hepatocytes and the extracutaneous disorder of symptoms.

Deterrence/Prevention:

- Deterrence and prevention of the cutaneous manifestations of HCV are the same as in acute HCV. The primary concerns are to avoid inoculation of the virus into healthy persons through contaminated blood and organs,

to prevent needlestick in at-risk groups (eg, health care workers), and to avoid high-risk behavior (eg, sharing cocaine-snorting straws and contaminated needles in pursuit of addictive drugs); all of these measures markedly reduce the likelihood of HCV infection.

Prognosis:

- The prognosis of patients with dermatologic manifestations of HCV infection rests on the success of therapy for the underlying HCV. At this time, many successes show that eradication of HCV infection is the key factor in the prognosis. The importance of discovering HCV infection magnifies as new therapies develop.

Patient Education:

- For excellent patient education resources, visit eMedicine's Skin, Hair, and Nails Center. Also, see eMedicine's patient education article Bruises.

Medical/Legal Pitfalls:

- Failure to diagnose an underlying condition and inappropriate or inadequate discovery and planning or treatment perpetuate HCV and create suboptimal care situations. The physician must decide how to proceed in situations in which underlying HCV is suggested by an existing history of risk factors. The physician must be comfortable with the level of skill in identifying HCV infection and must be aware of the success and failure of tests available to be willing to proceed with diagnosis. Likewise, individual cutaneous manifestations of HCV are uncommon and unfamiliar to many physicians. The severity of the disease makes early diagnosis and exacting care more critical.

- Failure of diagnosis leaves the physician at risk if proper care to diagnose or seek further help was not taken. Reading about HCV creates awareness of the possibility of HCV in at-risk patients, especially in patients who present with cutaneous or other extrahepatic manifestations consistent with HCV infection. Accurate and timely diagnosis of HCV is more critical as better drugs become available for the treatment of HCV. At-risk individuals with markers of HCV disease must be properly diagnosed.

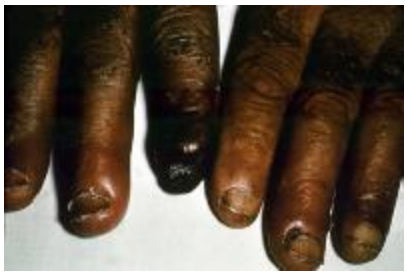
Special Concerns:

- Transmission from mother to child in utero relates to HIV/HBV co-infection and density of viral infection with HCV.

- While particle density of HCV infection of approximately 100 particles per milliliter produced no vertical transmission to the baby, 1 million HCV particles per milliliter resulted in a transmission rate of 36% (Ohto, 1994).

- Overall, transmission to babies was 6% in mothers who were HCV-antibody positive and 10% in mothers who were HCV-RNA positive.

Caption: Picture 1. Cold agglutinin disease indistinguishable from cryoglobulinemia. Courtesy of Walter Reed Army Medical Center Dermatology.



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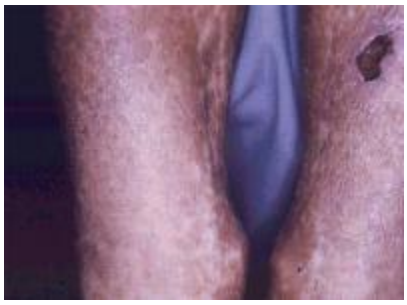
Caption: Picture 2. Cryoglobulinemia, palpable purpura, dysproteinemic purpura, and leukocytoclastic vasculitis (small vessel vasculitis). Courtesy of Walter Reed Army Medical Center Dermatology.



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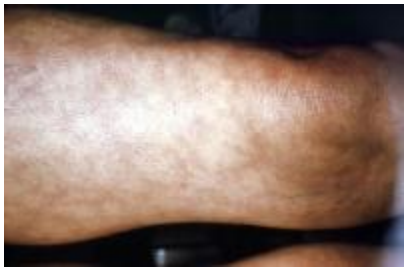
Caption: Picture 3. Cutis marmorata. Courtesy of Walter Reed Army Medical Center Dermatology.



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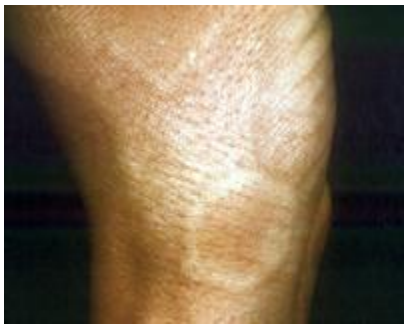
Caption: Picture 4. Erythema multiforme, bull's-eye lesions. Courtesy of Walter Reed Army Medical Center Dermatology.



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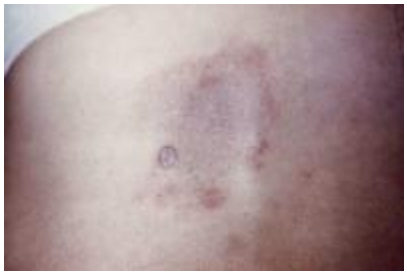
Caption: Picture 5. Erythema dyschromicum perstans. Courtesy of Walter Reed Army Medical Center Dermatology.



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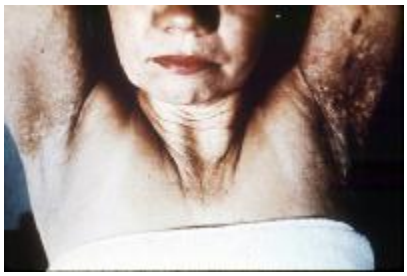
Picture Type: Photo

Caption: Picture 6. Erythema dyschromicum perstans. Courtesy of Walter Reed Army Medical Center Dermatology.



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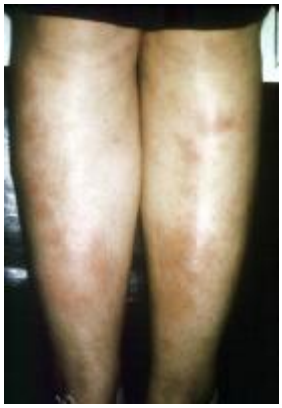
Caption: Picture 7. Erythema nodosa. Courtesy of Walter Reed Army Medical Center Dermatology.



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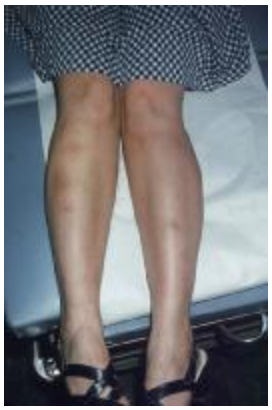
Caption: Picture 8. Erythema nodosa. Courtesy of Walter Reed Army Medical Center Dermatology.



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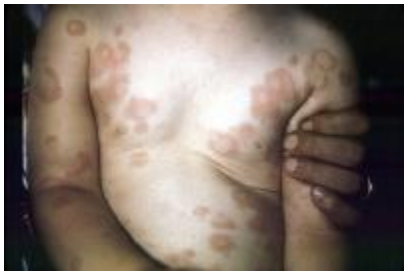
Caption: Picture 9. Erythema multiforme. Courtesy of Walter Reed Army Medical Center Dermatology.



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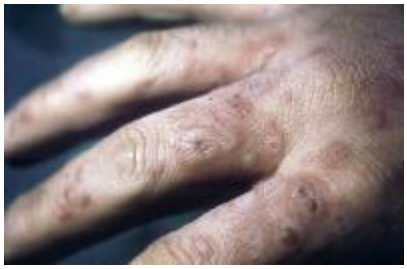
Caption: Picture 10. Erythema multiforme. Courtesy of Walter Reed Army Medical Center Dermatology.



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Caption: Picture 11. Erythema multiforme. Courtesy of Walter Reed Army Medical Center Dermatology.

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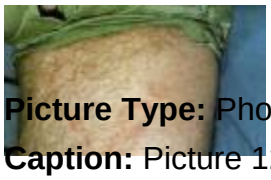

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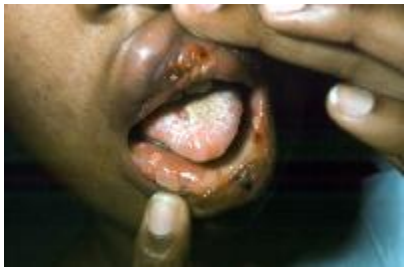
Picture Type: Photo

Caption: Picture 12. Erythema multiforme of the oral mucosa. Courtesy of Walter Reed Army Medical Center Dermatology.



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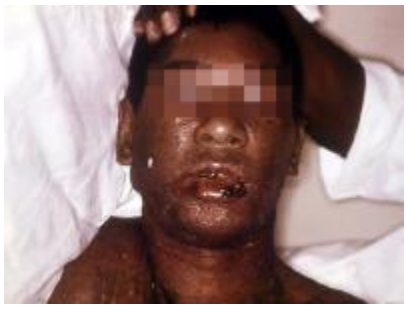
Caption: Picture 13. Erythema multiforme (Stevens-Johnson syndrome). Courtesy of Walter Reed Army Medical Center Dermatology.



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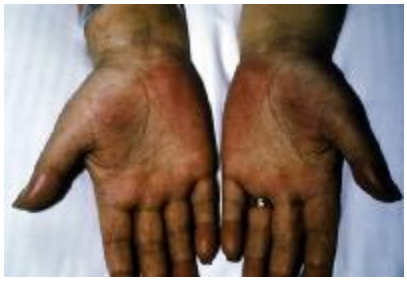
Caption: Picture 14. Palmar erythema. Courtesy of Walter Reed Army Medical Center Dermatology.



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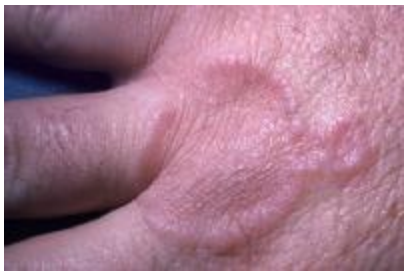
Caption: Picture 15. Granuloma annulare. Courtesy of Walter Reed Army Medical Center Dermatology.



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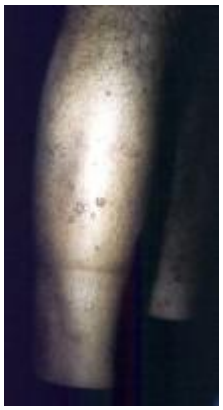
Picture Type: Photo

Caption: Picture 16. Disseminated superficial (actinic) keratosis. Courtesy of Walter Reed Army Medical Center Dermatology.



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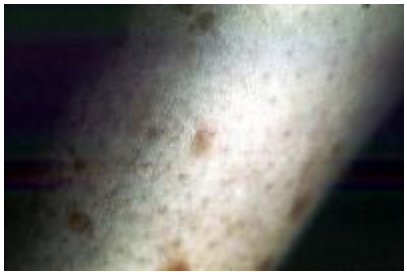
Picture Type: Photo

Caption: Picture 17. Disseminated superficial (actinic) keratosis. Courtesy of Walter Reed Army Medical Center Dermatology.



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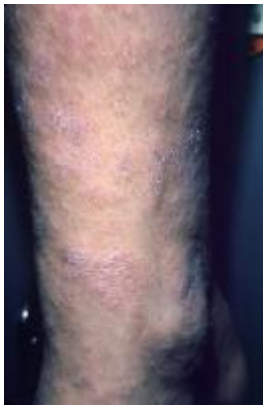
Picture Type: Photo

Caption: Picture 18. Lichen planus. Courtesy of Walter Reed Army Medical Center Dermatology.



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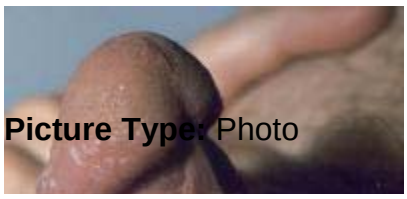
Picture Type: Photo

Caption: Picture 19. Lichen planus. Courtesy of Walter Reed Army Medical Center Dermatology.



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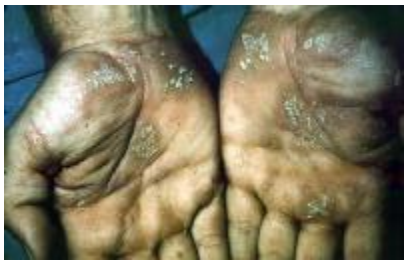
Picture Type: Photo

Caption: Picture 20. Lichen planus. Courtesy of Walter Reed Army Medical Center Dermatology.



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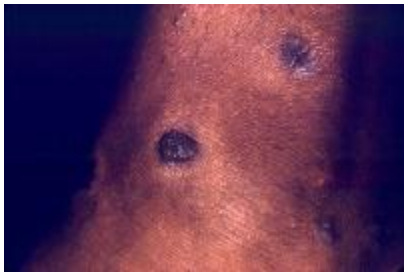
Picture Type: Photo

Caption: Picture 21. Lichen planus (hypertrophic type). Courtesy of Walter Reed Army Medical Center Dermatology.



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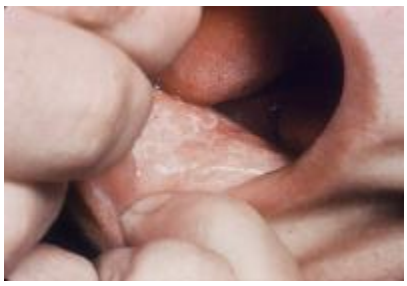
Picture Type: Photo

Caption: Picture 22. Lichen planus (oral lesions). Courtesy of Walter Reed Army Medical Center Dermatology.



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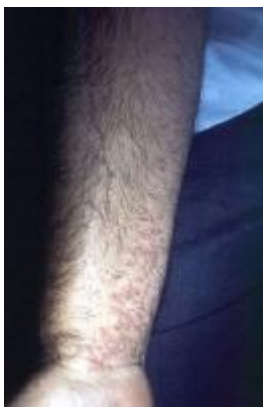
Picture Type: Photo

Caption: Picture 23. Lichen planus (volar wrist). Courtesy of Walter Reed Army Medical Center Dermatology.



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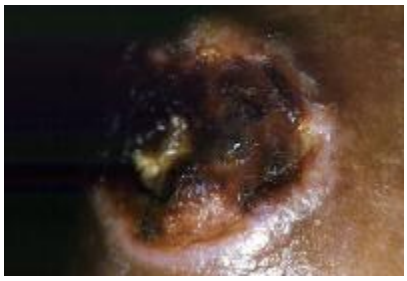
Picture Type: Photo

Caption: Picture 24. Lymphoma cutis. Courtesy of Walter Reed Army Medical Center Dermatology.



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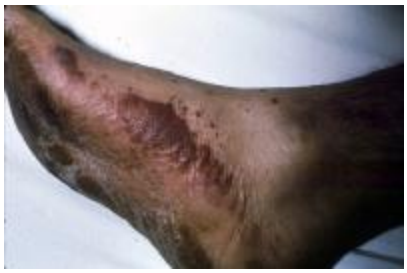
Picture Type: Photo

Caption: Picture 25. Henoch-Schönlein purpura. Courtesy of Walter Reed Army Medical Center Dermatology.



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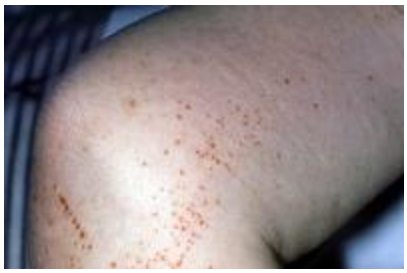
Picture Type: Photo

Caption: Picture 26. Palpable purpura. Courtesy of Walter Reed Army Medical Center Dermatology.



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Picture Type: Photo

Caption: Picture 27. Purpura in hemophilia (factor VIII deficiency). All ecchymoses and bland petechiae are in the differential diagnosis of thrombocytopenic purpuras, including thrombocytopenia secondary to hepatitis C virus in which an autoantibody to platelets is present. Courtesy of Walter Reed Army Medical Center Dermatology.

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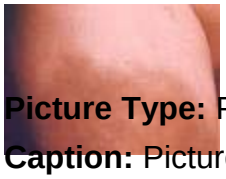
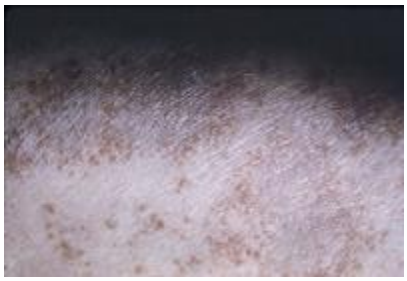


Picture Type: Photo

Caption: Picture 28. Progressive pigmented purpuric eruption. Courtesy of Walter Reed Army Medical Center Dermatology.



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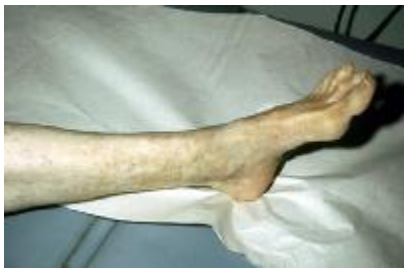
Picture Type: Photo

Caption: Picture 29. Progressive pigmented purpura (photo rotated 90°). Courtesy of Walter Reed Army Medical Center Dermatology.



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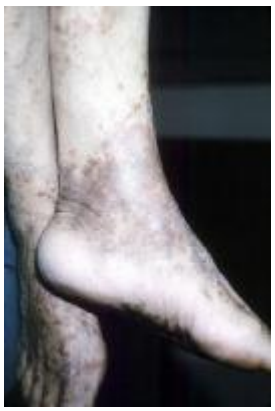
Picture Type: Photo

Caption: Picture 30. Progressive pigmented purpura (Gougerot-Blum disease). Courtesy of Walter Reed Army Medical Center Dermatology.



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Picture Type: Photo

Caption: Picture 31. Progressive pigmented purpura (Schamberg disease). Courtesy of Walter Reed Army Medical Center Dermatology.

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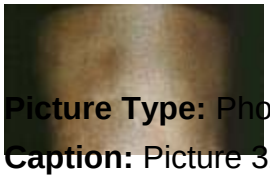

eMedicine Zoom View (Interactive!)

Picture Type: Photo

Caption: Picture 32. Thrombocytopenic purpura. Courtesy of Walter Reed Army Medical Center Dermatology.

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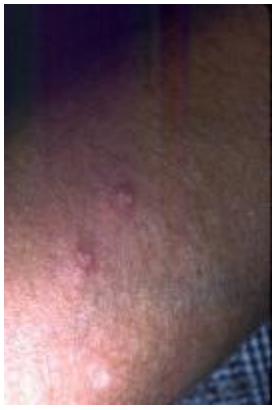
Picture Type: Photo

Caption: Picture 33. Prurigo nodularis. Courtesy of Walter Reed Army Medical Center Dermatology.



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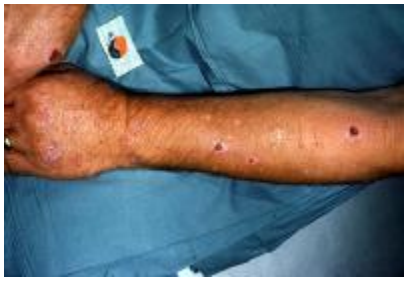
Picture Type: Photo

Caption: Picture 34. Prurigo nodularis. Courtesy of Walter Reed Army Medical Center Dermatology.



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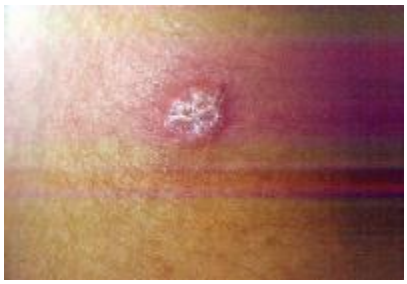
Picture Type: Photo

Caption: Picture 35. Prurigo nodularis. Courtesy of Walter Reed Army Medical Center Dermatology.



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Picture Type: Photo

Caption: Picture 36. Chronic urticaria. Courtesy of Walter Reed Army Medical Center Dermatology.

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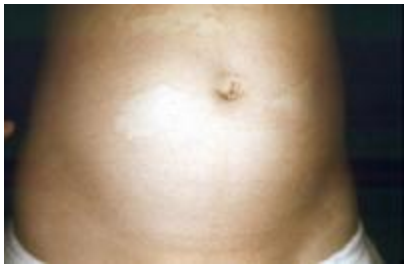
Picture Type: Photo

Caption: Picture 37. Urticaria (secondary to penicillin). Courtesy of Walter Reed Army Medical Center Dermatology.



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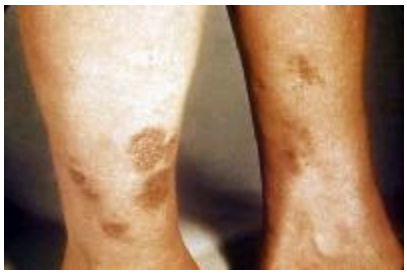
Picture Type: Photo

Caption: Picture 38. Nodular vasculitis. Courtesy of Walter Reed Army Medical Center Dermatology.



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Picture Type: Photo

Caption: Picture 39. Henoch-Schönlein purpura, palpable purpura, and leukocytoclastic vasculitis. Courtesy of Walter Reed Army Medical Center Dermatology.

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Picture Type: Photo

Caption: Picture 40. Vitiligo. Courtesy of Walter Reed Army Medical Center Dermatology.

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Picture Type: Photo

Caption: Picture 41. Vitiligo. Courtesy of Walter Reed Army Medical Center Dermatology.

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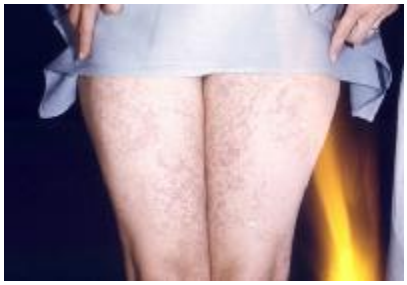
Picture Type: Photo

Caption: Picture 42. Waldenström hypergammaglobulinemic purpura. Courtesy of Walter Reed Army Medical Center Dermatology.



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