Extrahepatic manifestations of hepatitis C virus infection

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INTRODUCTION

Infection with hepatitis C virus (HCV) can lead to both acute and chronic hepatitis. In addition, there are several extrahepatic manifestations of chronic HCV infection, including [1-4]:

- Hematologic diseases such as cryoglobulinemia and lymphoma
- Autoimmune disorders such as thyroiditis
- Renal disease
- Dermatologic conditions such as lichen planus and porphyria cutanea tarda

Extrahepatic manifestations of HCV virus are common. In one series, 122 of 321 patients (38 percent) had at least one extrahepatic manifestation (table 1) [3]. In many cases, these manifestations appear to be directly related to the presence of the virus.

The extrahepatic manifestations of HCV infection will be reviewed here. The clinical manifestations of acute and chronic hepatitis due to HCV as well as the treatment of HCV are discussed separately. (See "Clinical manifestations and natural history of chronic hepatitis C virus infection" and "Overview of the management of chronic hepatitis C virus infection".)

GENERAL PRINCIPLES

Strength of disease associations — Chronic infection with hepatitis C virus (HCV) has been associated with numerous extrahepatic manifestations and diseases, although a direct link is

often difficult to establish. The most common extrahepatic findings with which the relationship to HCV infection is more strongly established are cryoglobulinemia, autoimmune disorders (including autoantibodies and sicca syndrome), porphyria cutanea tarda, and lichen planus. There also appears to be a clear association with B-cell non-Hodgkin lymphoma (particularly in patients with underlying cryoglobulinemia), but the incidence of lymphoma among HCV-infected patients overall remains low.

Evidence is also mounting that HCV is linked to diabetes mellitus, although the extent to which HCV infection itself rather than shared risk factors or comorbidities contribute to the association is unknown. Furthermore, because diabetes mellitus, as well as cardiovascular disease (with which HCV has been associated in some studies) are common and multifactorial, it is difficult to determine whether HCV is a major contributing factor in an individual patient.

Clinical implications — An understanding of the extrahepatic manifestations of HCV is important to inform testing for HCV with certain findings and to guide screening or monitoring for extrahepatic disease in HCV-infected individuals. Because of the associations, we advise testing for HCV infection in patients with the following manifestations:

- Cryoglobulinemia
- Porphyria cutanea tarda
- Lichen planus
- Necrolytic acral erythema
- Unexplained arthritis or false positive rheumatoid factor
- Sjögren's disease/sicca syndrome
- Membranoproliferative glomerulonephritis
- Idiopathic thrombocytopenic purpura

Diagnostic testing for HCV infection is discussed in detail elsewhere. (See "Screening and diagnosis of chronic hepatitis C virus infection", section on 'Diagnosis'.)

Conversely, extrahepatic manifestations can occur at any time during chronic infection with HCV, so patients diagnosed with chronic HCV infection should have evaluation for such manifestations at the initial visit and routinely during follow-up [5]. History of an HCV-infected patient should cover rheumatologic symptoms (eg, arthritis/arthralgias, dry eyes or mouth) and the physical exam should include a skin exam to evaluate for findings of cryoglobulinemia (eg, palpable purpura), porphyria cutanea tarda, and other associated dermatologic features. Laboratory testing should include a complete blood count, an assessment of renal function, evaluation for proteinuria and hematuria, and thyroid function testing. Cryoglobulins and complement levels should be checked if there is evidence of renal disease or other compatible

clinical findings. Workup for specific complaints, such as join pain or sicca symptoms, should include evaluation for associated syndromes as outlined below. Diagnosis of specific syndromes are discussed in the dedicated topic review.

Given the high efficacy and tolerability of interferon-free direct-acting antiviral therapies and the reductions in mortality and morbidity with successful eradication of HCV, treatment with such regimens is indicated for all chronically infected HCV-infected patients, with the exception of for those with limited life expectancy (eg, <12 months) due to unrelated conditions who would be unlikely to benefit from such treatment. The presence of extrahepatic manifestations, particularly those that are severe or highly symptomatic, is a reason to initiate antiviral treatment sooner than otherwise intended, as many extrahepatic findings improve or resolve with successful treatment of HCV infection.

LYMPHOPROLIFERATIVE DISORDERS

Hematologic disorders that have been associated with chronic hepatitis C virus (HCV) include essential mixed cryoglobulinemia, monoclonal gammopathies (which may be associated with multiple myeloma), and lymphoma.

Essential mixed cryoglobulinemia — Essential mixed cryoglobulinemia, also called type II cryoglobulinemia, is a lymphoproliferative disorder that can lead to the deposition of circulating immune complexes in small- to medium-sized blood vessels. More than 90 percent of patients with essential mixed cryoglobulinemia are infected with HCV, and about half of patients with HCV have cryoglobulins (69 of 127 in one study) (figure 1) [6]. As a result, all patients with chronic HCV should be evaluated for cryoglobulinemia. If either the history or the physical examination is suggestive of possible cryoglobulinemia, then the patient should undergo appropriate testing. All patients with mixed cryoglobulinemia should be tested for HCV infection. (See "Mixed cryoglobulinemia syndrome: Clinical manifestations and diagnosis", section on 'Infections' and "Mixed cryoglobulinemia syndrome: Clinical manifestations and diagnosis", section on 'Diagnosis'.).

The most common clinical manifestations include leukocytoclastic vasculitis (with palpable purpura and petechiae), arthralgias, renal disease (usually a membranoproliferative glomerulonephritis), neurologic disease, and hypocomplementemia. The purpura (picture 1) often involves the lower legs, may come in "crops," and can leave brown spots on the skin after it resolves. Skin biopsy demonstrates cutaneous vasculitis with dermal blood vessel destruction associated with a neutrophilic infiltration in and around the vessel wall (image 1A-B). (See

"Mixed cryoglobulinemia syndrome: Clinical manifestations and diagnosis" and "Evaluation of adults with cutaneous lesions of vasculitis", section on 'Skin biopsy to confirm vasculitis'.)

The vasculitis can result in ischemic necrosis and skin ulceration, rarely leading to necrosis of a digit. Other tissues, particularly the lower extremity peripheral nerves, may show similar vasculitic changes involving the vasa nervorum [7]. This may manifest clinically as a peripheral neuropathy that, as in other forms of vasculitis, is typically asymmetric (also called a mononeuritis multiplex). Lymphoma is an uncommon manifestation of cryoglobulinemia. (See "Mixed cryoglobulinemia syndrome: Clinical manifestations and diagnosis" and "Clinical manifestations and diagnosis of vasculitic neuropathies", section on 'Multiple mononeuropathy' and 'Lymphoma' below.)

Treatment of HCV can result in decreased cryoglobulin levels and improvements in skin lesions, renal function parameters, and other symptoms. As a result, prompt antiviral treatment should be considered in patients with symptoms related to cryoglobulinemia. Some patients with severe complications of cryoglobulinemia require additional therapy, such as plasmapheresis.

However, not all patients with HCV infection and cryoglobulinemia respond to anti-HCV therapy, and a reduction in cryoglobulin titers may not be directly associated with a decrease in serum alanine aminotransferase or HCV RNA levels. These issues are discussed elsewhere. (See "Treatment of chronic hepatitis C infection in adults with kidney function impairment", section on 'Rationale for antiviral treatment'.)

Lymphoma — HCV infection has been associated with the development of B-cell non-Hodgkin lymphoma (including diffuse large B-cell lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma, splenic lymphoma with villous lymphocytes, and extranodal marginal zone B cell lymphoma of mucosa-associated lymphoid tissue) as well as primary hepatic lymphoma [8-19]. The association between HCV and B-cell non-Hodgkin lymphoma is relatively well established, with a higher prevalence of HCV infection among lymphoma patients and vice versa, some evidence suggesting a decreased risk of lymphoma following treatment of HCV infection, and rare reports suggesting regression of lymphoma with antiviral treatment. The risk of lymphoma may be linked to cryoglobulinemia; the development of unexplained anemia or lymphadenopathy in a patient with HCV infection and clinically active cryoglobulinemia should raise concern about an underlying lymphoproliferative disorder [20]. Because of this association, it is reasonable to test patients with lymphoma for HCV infection.

Findings that support an association of HCV with lymphoma include:

- A meta-analysis that included 48 studies concluded that the prevalence of HCV in patients with B-cell non-Hodgkin lymphoma (NHL) was 15 percent, much higher than the

prevalence in the general population (around 1.5 percent) or in patients with other hematologic malignancies (3 percent) [8].

- A large cohort study of United States veterans published after the meta-analysis estimated the risk of NHL was increased by about 28 percent in patients with HCV (hazard ratio 1.28) compared with non-HCV-infected individuals [9]. The risk was also increased for Waldenstrom macroglobulinemia and cryoglobulinemia, but not other hematologic malignancies.

- A subsequent cohort study from Taiwan that included over 11,000 HCV-infected and 46,000 uninfected individuals found an increased risk of lymphoid neoplasms and NHL (adjusted hazard ratios 2.3 and 2.0, respectively) with HCV infection [21].

While not extensively studied, some data suggest that successful treatment of HCV may reduce the risk of lymphoma in patients who achieve a sustained virologic response. One of the largest studies included 3209 patients with HCV, of whom 2708 (84 percent) had received treatment with interferon-based therapy [22]. The overall annual incidence of lymphoma in patients with HCV was estimated to be 0.2 percent. The risk was reduced significantly in the 1048 patients who had achieved a sustained virologic response compared with those who had persistent infection (hazard ratio 0.13). (See "Overview of the management of chronic hepatitis C virus infection".)

Limited data also suggest the possibility of beneficial effects on the natural history of lymphoma with antiviral treatment. In one case report, remission of follicular lymphoma occurred following successful direct-acting-antiviral treatment for underlying HCV infection [23]. Regression of splenic lymphoma has also been described in association with interferon-based HCV treatment in a small case series [18]. (See "Splenic marginal zone lymphoma", section on 'Antiviral therapy for hepatitis C'.)

Lymphoma may develop due to the progression of cryoglobulinemia [17,20]. One hypothesis is that cryoglobulinemia arises from chronic stimulation of the immune system by HCV, predisposing to a lymphoproliferative disorder. While the steps leading to the development of a lymphoproliferative disorder are uncertain, an increased prevalence of the t(14;18) translocation in the B cells of patients with HCV may play a role [24-27]. Some HCV-associated lymphomas produce soluble immunoglobulins directed against the E2 protein (an HCV envelope glycoprotein) [28]. This observation supports the hypothesis that some HCV-associated lymphomas originate from B cells that were initially activated by the HCV-E2 protein. (See "Clinical manifestations, pathologic features, diagnosis, and prognosis of follicular lymphoma", section on 'Cytogenetics'.)

In addition, HCV infection may increase the risk of hepatotoxicity related to treatment for lymphoma. In a study of 553 patients, the presence of HCV infection predicted severe hepatoxicity in patients with diffuse large B-cell lymphoma who were treated with rituximab-containing chemotherapy regimens (hazard ratio 15) [29].

Monoclonal gammopathies — Chronic HCV infection may be a risk factor for the development of monoclonal gammopathies; however, the association is unclear, and monoclonal gammopathy is not rare in the general population over the age of 50 years. Prior to the development of HCV tests, the prevalence of monoclonal gammopathies was noted to be increased in patients with chronic liver disease [30]. Routine screening of patients with HCV for monoclonal gammopathies is not recommended. (See "Diagnosis of monoclonal gammopathy of undetermined significance".)

The results of studies looking at the association of HCV with monoclonal gammopathies have been variable:

- One study of patients with chronic liver disease compared 239 HCV-positive patients with 98 HCV-negative controls (76 with chronic hepatitis B, 9 with alcoholic liver disease, and 13 with primary biliary cholangitis) [31]. Monoclonal bands were more common in patients with HCV compared with age-matched controls (11 versus 1 percent). Of the 26 patients with monoclonal bands, 9 (35 percent) had either smoldering myeloma or multiple myeloma. The incidence of monoclonal gammopathies peaked in patients between the ages of 60 and 69 years (21 percent). Of the patients with monoclonal gammopathies, 50 percent had HCV genotype 2a/c, which was significantly higher than the prevalence in the matched controls (18 percent).

- A second study of 824 patients with chronic liver disease (530 with HCV and 294 with other liver diseases) found that 12 percent of the HCV-positive patients had a monoclonal band, compared with 3 percent of the control patients [32]. Like the earlier study, this study also showed an increase in the prevalence of HCV genotype 2a among patients with monoclonal gammopathies.

- However, other studies have failed to show an association of monoclonal gammopathies with HCV infection [33,34]. For example, one study of 100 patients with HCV found no cases of monoclonal gammopathy [33].

In addition to monoclonal gammopathies, HCV has also been associated with polyclonal or oligoclonal hyperglobulinemia (most often IgG) [35,36]. In these patients, gammaglobulin levels correlate with the disease severity seen on liver biopsy. Serum gammaglobulin levels have been noted to decrease following successful treatment for HCV.

DERMATOLOGIC DISEASE

A variety of dermatologic diseases are associated with hepatitis C virus (HCV) infection [37]. The dermatologic response to treatment of the underlying HCV is variable [38].

Porphyria cutanea tarda — Porphyria cutanea tarda (PCT) is a disease caused by markedly reduced activity of hepatic uroporphyrinogen decarboxylase (UROD), resulting in accumulation of uroporphyrins and other highly carboxylated porphyrins in the liver, as well as the blood and urine (figure 2) [39]. PCT is characterized by chronic blistering photosensitivity and skin fragility; exposure to the sun and/or minor trauma can lead to skin erythema, vesicles, and bullae, which may become hemorrhagic (picture 2). Transaminases are often elevated, but neurovisceral attacks (eg, abdominal pain, neuropsychiatric changes) do not occur. The clinical manifestations and diagnosis of PCT are discussed in detail elsewhere. (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis", section on 'Clinical features' and "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis", section on 'Diagnostic evaluation'.)

HCV infection is strongly associated with PCT. As an example, a systematic review of 50 studies that included a total of 2167 patients with PCT found an overall prevalence of HCV of 50 percent [40]. However, there was marked geographic variability, corresponding to variability in baseline rates of HCV infection in the general population. The precise mechanism for the increased risk of PCT with HCV infection is unknown. (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Pathogenesis, clinical manifestations, and diagnosis", section on 'HCV infection'.)

All patients with PCT should be tested for HCV infection, as well as other potential disease associations, including HIV infection, iron overload, and hemochromatosis (with *HFE* mutation testing). In patients with chronic HCV infection, PCT often, but not always, improves with clearance of HCV viremia with antiviral therapy. Primary therapies for active PCT skin lesions are discussed in detail elsewhere. (See "Porphyria cutanea tarda and hepatoerythropoietic porphyria: Management and prognosis".)

Antiviral regimens for chronic HCV infection are also discussed elsewhere. (See "Management of chronic hepatitis C virus infection: Initial antiviral therapy in adults" and "Management of chronic hepatitis C virus infection: Antiviral retreatment following relapse in adults".)

Lichen planus — Lichen planus (LP) is characterized by flat-topped, violaceous, pruritic papules with a generalized distribution (picture 3). It can also involve mucus membranes, hair, and nails. Because of the frequency with which HCV infection has been reported among patients

with lichen planus in some geographic locations, we advise testing for HCV in patients with lichen planus. (See "Lichen planus".)

Lichen planus can be seen in patients with a variety of liver diseases, particularly advanced liver disease. Systematic reviews have reported that patients with oral lichen planus are approximately two to six times more likely to have reactive anti-HCV antibodies compared with controls, although there is substantial geographical heterogeneity to the findings [41-43]. In some studies, the prevalence of anti-HCV antibodies in patients with lichen planus ranges from 10 to 40 percent [1]. There is evidence of a genetic risk for HCV-associated lichen planus [44]. There are also reports of the development or exacerbation of lichen planus during interferon treatment for chronic HCV infection. The impact on lichen planus of interferon-free direct-acting antiviral treatment of HCV is uncertain.

Necrolytic acral erythema — Necrolytic acral erythema is a pruritic, psoriasis-like skin disease characterized by sharply marginated, erythematous to hyperpigmented plaques with variable scale and erosion on the lower extremities (picture 4). In a series of 30 patients who presented with the disorder, all were found to have antibodies to HCV [45]. All patients with necrolytic acral erythema should be tested for HCV infection.

Biopsy specimens showed psoriasiform changes, keratinocyte necrosis, and papillomatosis. Improvement was observed in a patient who had been treated for HCV with interferon who subsequently relapsed nine months after therapy was discontinued. Topical and systemic corticosteroids have a variable benefits. Other reports have confirmed improvement with interferon-alfa and also suggest a benefit from oral zinc sulfate [46-49].

Leukocytoclastic vasculitis — A leukocytoclastic vasculitis can occur in conjunction with essential mixed cryoglobulinemia, presenting clinically with palpable purpura and petechiae that usually involve the lower extremities. (See 'Essential mixed cryoglobulinemia' above.)

AUTOIMMUNE DISORDERS

A number of autoimmune disorders have been associated with chronic hepatitis C virus (HCV) infection, including subclinical autoantibody formation, thyroid disease, sialadenitis, and autoimmune thrombocytopenic purpura.

In an analysis of 1020 patients with HCV infection in an international registry, autoimmune disorders that were present included Sjögren's disease (48 percent), rheumatoid arthritis (15 percent), systemic lupus erythematosus (13 percent), polyarteritis nodosa (8 percent), and antiphospholipid syndrome (6 percent) [50]. Many of the patients had antinuclear antibodies (61

percent), rheumatoid factor (57 percent), hypocomplementemia (52 percent), and/or cryoglobulins (52 percent).

Asymptomatic autoantibodies — Autoantibodies are common in patients with chronic HCV infection. Antinuclear antibodies, antibodies directed against the Fc portion of IgG (rheumatoid factor), anticardiolipin antibodies, smooth muscle antibodies, or antithyroid antibodies are detected in 40 to 65 percent of patients [3,50-52]. While antibodies are often present in low titers, do not appear to influence the presentation or course of the infection, and are not associated with extrahepatic disease, autoimmune hepatitis and thyroid disease (primarily hypothyroidism) have been associated with chronic HCV infections. (See 'Autoimmune hepatitis' below and 'Thyroid disease' below.)

The presence of autoantibodies may result in diagnostic difficulties. For example, an HCV-infected patient with arthralgias, arthritis, and rheumatoid factor positivity may be misdiagnosed initially as having rheumatoid arthritis (RA). In this setting, testing for other RA-associated autoantibodies that are observed infrequently in patients with HCV infection, such as anti-citrullinated peptide (eg, anti-cyclic citrullinated peptide or CCP) antibodies, may be helpful diagnostically [53]. We advise testing for HCV infection in patients with an isolated positive rheumatoid factor. (See "Rheumatoid factor: Biology and utility of measurement".)

Among patients who are treated with an interferon-containing regimen, autoantibodies may first become detectable or increase in titer during treatment. However, their presence does not affect the disease course or the response to treatment.

Sjögren's disease/sicca symptoms — A lymphocytic sialadenitis with sicca symptoms suggestive of Sjögren's disease has been described in patients with chronic HCV infection [54-56], and we advise testing for HCV infection in patients with Sjögren's disease. In a systematic review, the prevalence of Sjögren-like symptoms was 12 percent among HCV-infected patients compared with less than 1 percent among uninfected controls [43]. Furthermore, a study of 137 patients with Sjögren's disease and HCV infection suggested that the clinical and immunologic features were indistinguishable from Sjögren's disease in patients without HCV [55]. However, in a subsequent study of patients with Sjögren's disease, markers of cryoglobulinemia were higher and anti-La and Ro antibodies were lower among those with HCV infection compared with those without [57]. Histologically, patients with HCV often have mild sialadenitis with pericapillary lymphocytic infiltration (rather than periductal) with no destruction of the salivary gland ducts. (See "Clinical manifestations of Sjögren's disease: Exocrine gland disease".)

Autoimmune hepatitis — Unlike some of the other autoantibodies seen in HCV that do not have clinical significance, antibodies to actin and to liver/kidney microsomes (anti-LKM-1) may

be clinically significant. These antibodies are characteristic of types 1 and 2 autoimmune hepatitis, respectively, and have been detected in some patients with chronic HCV infection, particularly in Europe [58-60], although it is not recommended that patients be routinely screened for these antibodies. (See "Overview of autoimmune hepatitis" and "Overview of autoimmune hepatitis", section on 'Autoantibodies'.)

Determining the primary cause of the patient's hepatitis can be difficult in patients with both HCV and anti-LKM-1 antibodies. The anti-LKM-1 antibodies in patients with HCV are directed at different epitopes of cytochrome P450 2D6 (CYP2D6, the target antigen) than the antibodies in patients with autoimmune hepatitis [61,62], which may help differentiate between patients whose hepatitis is due primarily to HCV and patients whose hepatitis is due to autoimmune hepatitis.

Most patients with HCV and anti-LKM-1 antibodies appear to benefit from antiviral therapy to the same extent as patients with chronic HCV without such antibodies. If such patients are treated with an interferon-containing regimen, however, close monitoring during interferon treatment is required since flares of aminotransferases without subsequent clearance of HCV RNA have been observed [63,64]. Some of these patients will respond to treatment for autoimmune hepatitis with prednisone and azathioprine [65,66].

Thyroid disease — Thyroid disorders are common in patients with HCV infection, particularly women [67,68]. Overall, antithyroid antibodies are present in 5 to 17 percent of patients infected with HCV, and thyroid disease (primarily hypothyroidism) occurs in 2 to 13 percent of patients [67,68]. The highest prevalence of both thyroid antibodies and thyroid disease is found in older women. However, whether or not the prevalence is higher than in age- and sex-matched controls is controversial [69,70]. Thyroid function tests should be checked when a patient is first diagnosed with HCV. Patients found to be hypothyroid should receive thyroid hormone replacement. (See "Diagnosis of and screening for hypothyroidism in nonpregnant adults" and "Treatment of primary hypothyroidism in adults".)

One of the largest studies of thyroid disease in patients with HCV included 630 consecutive patients with HCV (without cirrhosis) who were compared with 389 subjects from an iodine-deficient area, 286 subjects from an area of iodine sufficiency, and 86 patients with chronic hepatitis B virus infection [68]. Mean thyroid stimulating hormone levels were significantly higher and free T3 and T4 levels significantly lower in patients with HCV compared with the other groups. Patients with HCV were more likely than controls to have hypothyroidism (13 versus 3 to 5 percent), anti-thyroglobulin antibodies (17 versus 9 to 10 percent), and anti-thyroperoxidase antibodies (21 versus 10 to 13 percent). As with other autoimmune phenomena, thyroid disease can also develop in patients with HCV infection who are treated

with interferon. (See "Laboratory assessment of thyroid function" and "Pathogenesis of Hashimoto's thyroiditis (chronic autoimmune thyroiditis)".)

Immune thrombocytopenia (ITP) and autoimmune hemolytic anemia — A number of studies have suggested an association between HCV infection and immune thrombocytopenia (ITP) and/or autoimmune hemolytic anemia, either as a consequence of interferon therapy or in the setting of chronic infection without therapy [71,72]. One of the largest studies included 120,691 United States veterans with chronic HCV who were matched with 454,905 controls [72]. HCV was associated with ITP in both treated and untreated patients (hazard ratio [HR] 1.8). An increased risk of autoimmune hemolytic anemia was also detected (HR 2.8), but only in patients who were treated with interferon-based therapy. (See "Immune thrombocytopenia (ITP) in adults: Clinical manifestations and diagnosis" and "Diagnosis of hemolytic anemia in adults".)

Thrombocytopenia in patients with chronic HCV infection may also be related to chronic liver disease. (See "Hemostatic abnormalities in patients with liver disease", section on 'Thrombocytopenia and platelet dysfunction'.)

DIABETES MELLITUS

Hepatitis C virus (HCV) infection has been linked to diabetes mellitus in several studies [73-82]. A meta-analysis of 34 studies estimated that the risk was increased by almost 70 percent in HCV-infected patients compared with non-infected controls (OR 1.7) [83]. The risk was also increased compared with patients who had chronic hepatitis B virus infection. However, routine screening for diabetes mellitus is not recommended based upon the presence of HCV alone. (See "Screening for type 2 diabetes mellitus".)

Some studies have identified risk factors for the development of diabetes mellitus in HCV-infected patients, such as older age, obesity, severe liver fibrosis, and a family history of diabetes mellitus [84]. Patients undergoing liver transplantation for HCV also appear to be at increased risk of developing diabetes mellitus following transplantation compared with patients undergoing transplantation for other indications [85].

The cause of the association of HCV with diabetes is unknown. In addition, the magnitude of the association may be overestimated because [86]:

- Patients with diabetes have more parenteral exposures than the general population, placing them at increased risk for transmission of viruses.

- Not all studies controlled for the presence of cirrhosis, which may be associated with impaired glucose tolerance.

HCV has also been linked to insulin resistance without overt diabetes [87,88]. Insulin resistance may contribute to hepatic fibrosis progression, particularly with HCV genotypes 1 and 4 and with high serum RNA levels [87,89].

Successful HCV treatment may decrease the risk of diabetes mellitus. In at least two reports, achievement of a sustained virologic response with interferon-based therapy was associated with a reduced incidence of diabetes mellitus [90,91]. In another report, insulin resistance decreased in patients who achieved an SVR but not in patients who failed to respond to treatment or relapsed [92].

OTHER MANIFESTATIONS

Ocular disease — Hepatitis C virus (HCV) infection has been associated with a variety of ophthalmologic disorders including dry eyes, corneal ulcers (Mooren's ulcer), uveitis, scleritis, and, in patients with HCV-related Sjögren's disease/sicca symptoms [55,93-96] (see 'Sjögren's disease/sicca symptoms' above). In addition, ophthalmologic disorders (retinal hemorrhages, cotton wool spots, and, rarely, retinal artery or vein obstruction) have been reported during interferon therapy.

Renal disease — Glomerular disease may occur in patients with chronic HCV infection. The pathogenesis appears to be related to the deposition of immune complexes containing anti-HCV and HCV RNA in the glomeruli. The most common patterns are membranoproliferative glomerulonephritis (usually associated with essential mixed cryoglobulinemia) and, less frequently, membranous nephropathy [97,98]. Several series have reported that anti-HCV antibodies are nearly universal in patients with both membranoproliferative glomerulonephritis and cryoglobulinemia. (See "Overview of kidney disease associated with hepatitis C virus infection".)

The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend screening for kidney disease at the time of HCV diagnosis and then annually thereafter with urinalysis and serum creatinine [99].

Antiviral HCV treatment is indicated in patients with membranoproliferative glomerulonephritis. A number of studies have reported a beneficial response to antiviral therapy in this setting, and the reduction in proteinuria correlates with a fall in HCV RNA [97,100,101]. However, renal

function is not always improved by treatment. (See "Overview of kidney disease associated with hepatitis C virus infection".)

Musculoskeletal — Cross-sectional studies have found an association of HCV with decreased bone mineral density and fractures (hepatic osteodystrophy) [102-107]. The mechanism may be related to chronic inflammation and liver dysfunction [103,108,109]. In a study of Medicaid recipients, the risk of hip fracture was higher among those with HCV than those who were uninfected (2.7 versus 1.9 events/1000 person-years) [107]. The risk was highest among those coinfected with HCV and HIV (3.1 events/1000 person-years).

HCV-associated osteosclerosis is a rare disorder characterized by a marked increase in bone mass during adult life. While most cases have been reported in patients with a history of intravenous drug abuse, it has also been seen with HCV infection from blood transfusion [110]. Periosteal, endosteal, and trabecular bone thickening occur throughout the skeleton, with the exception of the cranium. During active disease, forearm and leg pain are common, bone remodeling (turnover) is high, and bone mineral density is two- to threefold higher than age-matched norms. The increased remodeling may respond to bisphosphonates or calcitonin, but spontaneous remission has also been described. Abnormalities in insulin-like growth factors (IGF-1 and IGF-2) or their binding proteins may contribute to the increase in bone formation in this disorder [111].

Arthritis is noted in 2 to 20 percent of patients with HCV. It is a rheumatoid-like arthritis in two-thirds of the cases and an oligoarthritis in the rest. (See "Clinical manifestations of rheumatoid arthritis", section on 'Typical 'classic' RA'.)

The possibility of cryoglobulinemia should be considered in patients with HCV infection who have arthralgias or myalgias. (See 'Essential mixed cryoglobulinemia' above.)

Cardiac and cardiovascular disease — Although data from individual cohorts have not been consistent, evidence overall suggests that chronic HCV infection is associated with adverse cardiovascular outcomes [112]. In a meta-analysis, HCV-infected patients had higher rates of cardiovascular death (OR 1.65, 95% CI 1.07-2.56 in three studies) and cerebro- and cardiovascular events (OR 1.30, 95% CI 1.10-1.55 in eight studies) [113]. Data among HIV-infected patients has also been mixed, with some but not all studies indicating an increased risk of cardiovascular disease with HCV coinfection. (See "Epidemiology of cardiovascular disease and risk factors in patients with HIV", section on 'Hepatitis C virus infection'.)

HCV has also been associated with myocarditis and cardiomyopathy in reports from Japan. The pathogenesis is unclear. (See "Myocarditis: Causes and pathogenesis", section on 'Viral or "idiopathic" myocarditis' and "Myocarditis: Causes and pathogenesis", section on 'Hepatitis C'.)

Other hematologic disorders — Some studies have also identified an association with venous thromboembolism [114]. (See "Hemostatic abnormalities in patients with liver disease", section on 'VTE risk'.)

Neurologic and neuropsychiatric disease — Symptoms of fatigue and deficits in concentration and working memory are commonly reported in patients with chronic HCV infection. Some studies have suggested such neurocognitive impairments are associated with HCV, even after controlling for other comorbid conditions, such as substance abuse, affective disorders, and cirrhosis [115-117]. Functional imaging studies have also identified metabolic changes in the central nervous system in the setting of HCV infection. Coinfection with HCV is also a potential risk factor for HIV-associated neurocognitive disorder. (See "HIV-associated neurocognitive disorders: Epidemiology, clinical manifestations, and diagnosis", section on 'Comorbidities'.)

Other neurologic conditions linked to HCV infection include Parkinson disease [118].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis C virus infection".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Hepatitis C (The Basics)")

- Beyond the Basics topics (see "Patient education: Hepatitis C (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Hepatitis C virus (HCV) infection is associated with several extrahepatic manifestations. In many cases, these manifestations appear to be directly related to the presence of the virus, although a direct link is often difficult to establish. Because of the potential association, patients with the following syndromes should undergo testing for HCV infection (see 'Strength of disease associations' above and 'Clinical implications' above):
  - Cryoglobulinemia
  - Porphyria cutanea tarda
  - Lichen planus
  - Necrolytic acral erythema
  - Unexplained arthritis or false positive rheumatoid factor
  - Sjögren's disease/sicca symptoms
  - Membranoproliferative glomerulonephritis
  - Idiopathic thrombocytopenic purpura compare
- History and physical exam of HCV-infected patients should include assessment for common extrahepatic manifestations, including rheumatologic symptoms (eg, arthritis/arthralgias, dry eyes or mouth), cryoglobulinemia (eg, palpable purpura), porphyria cutanea tarda, and other dermatologic abnormalities. Laboratory testing should include a complete blood count, an assessment of renal function, evaluation for proteinuria and hematuria, and thyroid function testing. Cryoglobulins and complement levels should be checked if there is evidence of renal disease or other compatible clinical findings of cryoglobulinemia. Testing for other extrahepatic manifestations of HCV infection should be guided by symptoms or specific physical findings. (See 'Clinical implications' above.)
- The most common or most strongly associated extrahepatic manifestations of HCV include:
  - Essential mixed cryoglobulinemia – More than 90 percent of patients with essential mixed cryoglobulinemia are infected with HCV, and about half of patients with HCV have cryoglobulins. The most common clinical manifestations include leukocytoclastic vasculitis (with palpable purpura and petechiae (picture 1)), arthralgias, membranoproliferative glomerulonephritis, neurologic disease, and

hypocomplementemia. Treatment of HCV can result in decreased cryoglobulin levels and improvements in skin lesions, renal function parameters, and other symptoms. (See 'Essential mixed cryoglobulinemia' above.)

- B-cell non-Hodgkin and primary hepatic lymphomas – The association between HCV and these lymphomas is relatively well established, with a higher prevalence of HCV infection among lymphoma patients and vice versa, some evidence suggesting a decreased risk of lymphoma following treatment of HCV infection, and rare reports suggesting regression of lymphoma with antiviral treatment. The risk of lymphoma may be linked to cryoglobulinemia. (See 'Lymphoma' above.)

- Porphyria cutanea tarda (PCT) – About half of patients with the sporadic form of PCT have evidence of HCV infection, although with marked geographic variability in prevalence. Skin disease is characterized by chronic blistering photosensitivity and skin fragility (picture 2). PCT is treated with phlebotomy or hydroxychloroquine, and often, but not always, improves with clearance of HCV viremia. (See 'Porphyria cutanea tarda' above.)

- Other dermatologic manifestations – Lichen planus (picture 3) and necrolytic acral erythema (picture 4) are strongly associated with HCV infection. (See 'Lichen planus' above and 'Necrolytic acral erythema' above.)

- Autoimmune disorders – Subclinical autoantibody formation, Sjögren's disease with sicca symptoms, thyroid disease, and autoimmune thrombocytopenic purpura have all been associated with chronic HCV infection. (See 'Autoimmune disorders' above.)

- HCV infection has been linked to the development of diabetes mellitus, with a nearly 70 percent increased relative risk among HCV-infected individuals. Limited evidence suggests that successful HCV treatment decreases the risk of diabetes mellitus. (See 'Diabetes mellitus' above.)

- A variety of other extrahepatic manifestations potentially associated with HCV have been described, including ocular diseases, other renal diseases, musculoskeletal disorders, cardiovascular disease, and neurocognitive dysfunction. (See 'Other manifestations' above.)

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Topic 3676 Version 36.0

GRAPHICS

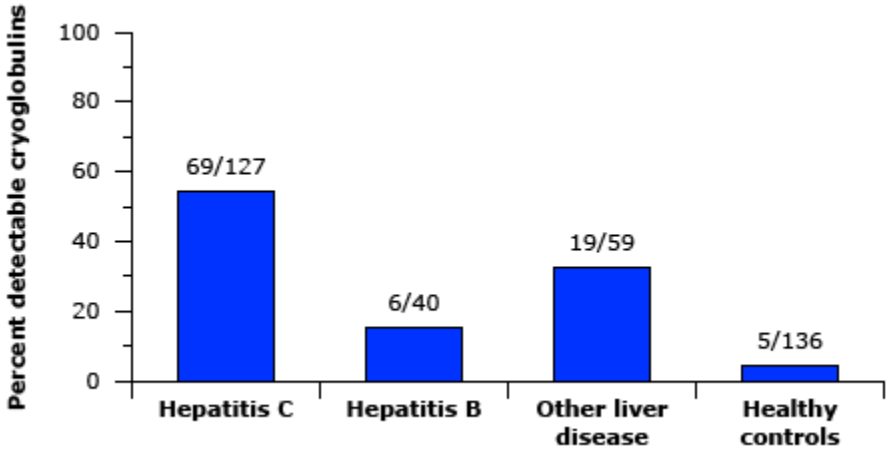
Prevalence of clinical extrahepatic manifestations in 321 patients with chronic HCV infection

	N (percent)
Skin involvement	
Purpura	21 (7)
Raynaud phenomenon	21 (7)
Cutaneous vasculitis	19 (6)
Pruritus	20 (6)
Psoriasis	6 (20)
Porphyria cutanea tarda	3 (1)
Lichen planus	3 (1)
At least one skin manifestation	55 (17)
Rheumatologic involvement	
Arthralgia	60 (19)
Arthritis	6 (2)
Myalgia	31 (2)
Neurologic involvement	
Sensory neuropathy	28 (9)
Motor neuropathy	15 (5)
Miscellaneous	
Sicca syndrome (mouth)	40 (12)
Sicca syndrome (eye)	32 (10)
Hypertension	32 (10)
Uveitis	2 (1)
Overall	
At least one extrahepatic clinical manifestation	122 (38)

Data from: Cacoub P, Renou C, Rosenthal E, et al. Medicine 2000; 79:47.

Graphic 66842 Version 2.0

Incidence of cryoglobulins in chronic liver disease

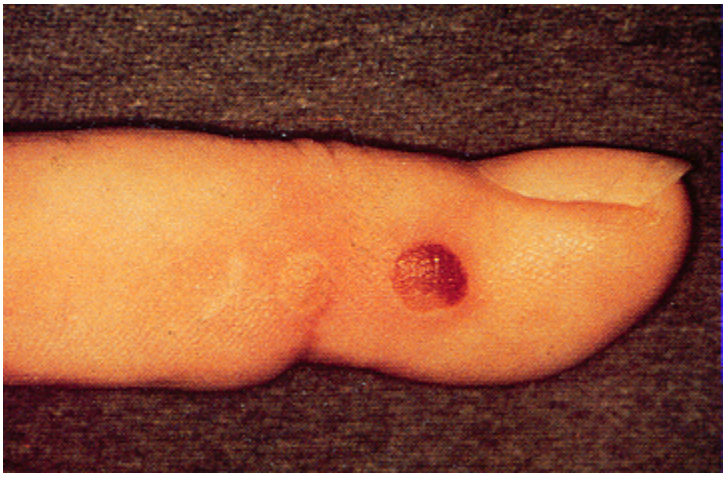


Incidence of circulating cryoglobulins in 136 healthy controls and in 226 patients with chronic liver disease due to hepatitis C, hepatitis B, or other liver diseases (such as autoimmune hepatitis and primary biliary cholangitis). Cryoglobulins were unusual in controls and most common in patients with hepatitis C virus infection, being detected in 54% of cases.

Data from: Lunel F, Musset L, Cacoub P, et al. Cryoglobulinemia in chronic liver diseases: Role of hepatitis C virus and liver damage. Gastroenterology 1994; 106:1291.

Graphic 80075 Version 5.0

Leukocytoclastic vasculitis

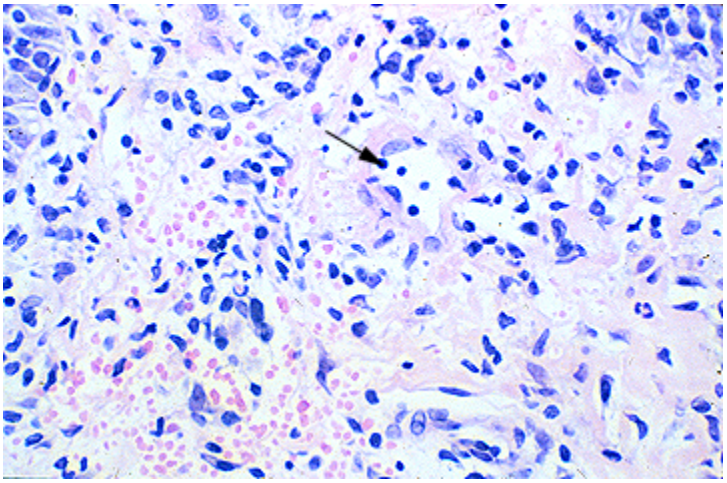


Leukocytoclastic vasculitis appearing as raised purpura. This lesion can occur with any vasculitic syndrome and in the collagen vascular diseases.

Courtesy of Marvin I Schwarz, MD.

Graphic 78697 Version 2.0

Leukocytoclastic vasculitis histology

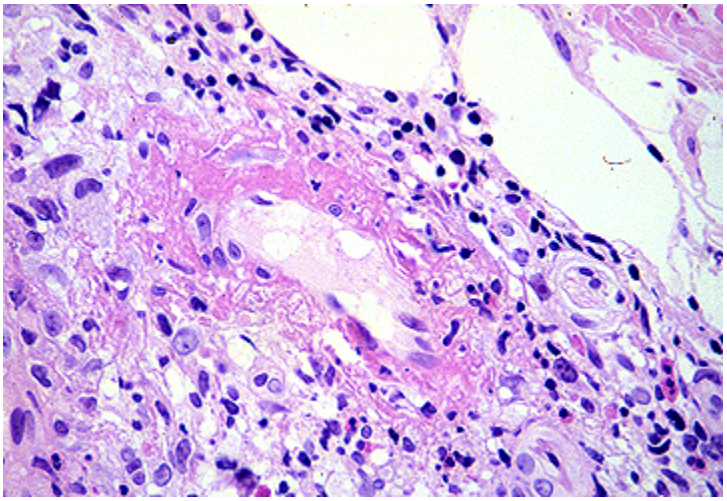


Leukocytoclastic vasculitis involving the dermal papillae capillaries and venules (arrow), a finding that probably reflects an Arthus type III immune complex reaction.

Courtesy of Cynthia Magro, MD.

Graphic 52548 Version 3.0

Leukocytoclastic vasculitis histology

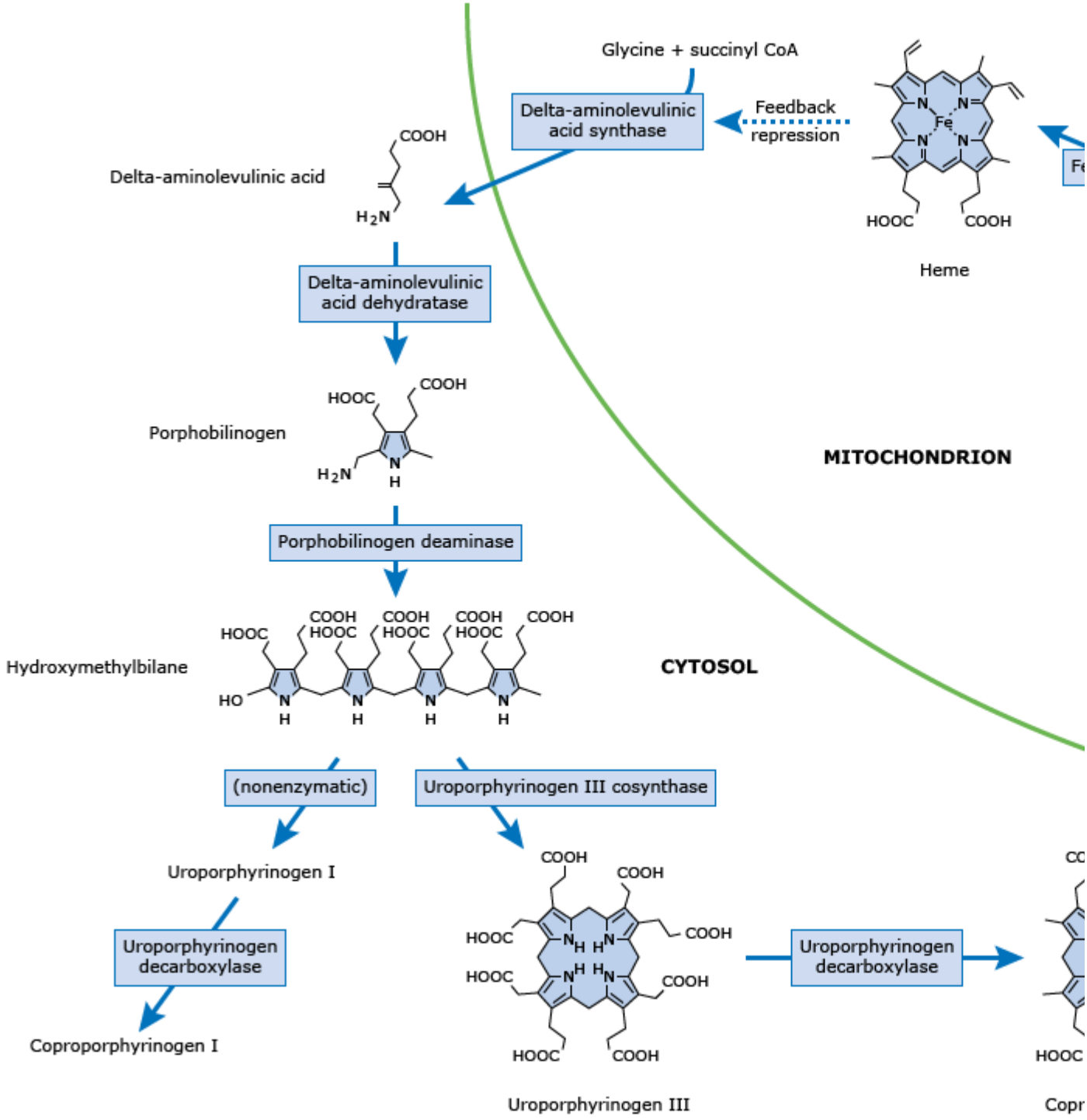


Skin biopsy from a patient with leukocytoclastic vasculitis showing striking mural fibrin deposition in a postcapillary venule and a concomitant angiocentric mixed neutrophilic and lymphocytic infiltrate. This pattern can be seen in a variety of disorders including hypersensitivity vasculitis, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, Sjögren's disease, Behçet syndrome, and relapsing polychondritis.

Courtesy of Cynthia Magro, MD.

Graphic 66296 Version 9.0

Heme biosynthesis pathway showing chemical intermediates and sites of prod



Heme synthesis begins with the formation of delta-aminolevulinic acid (ALA) from glycine and succinyl-CoA b in the liver. Hepatic ALAS is mainly regulated by heme via feedback repression (dashed arrow at the top of th porphyrias that result from deficiencies of these enzymes.

CoA: coenzyme A.

Reproduced from: Anderson KE. The porphyrias. In: Zakim and Boyer's Hepatology: A Textbook of Liver Disease, 5th ed, Boyer TD, Wrig

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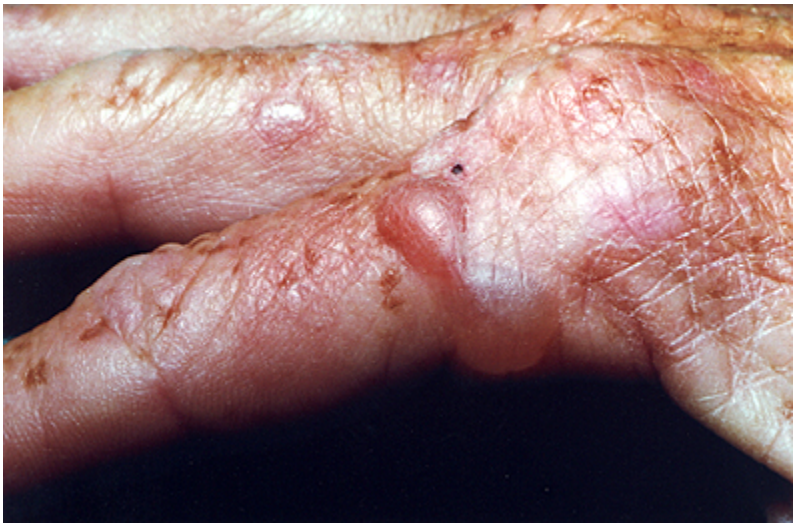
Graphic 117995 Version 1.0

Porphyria cutanea tarda

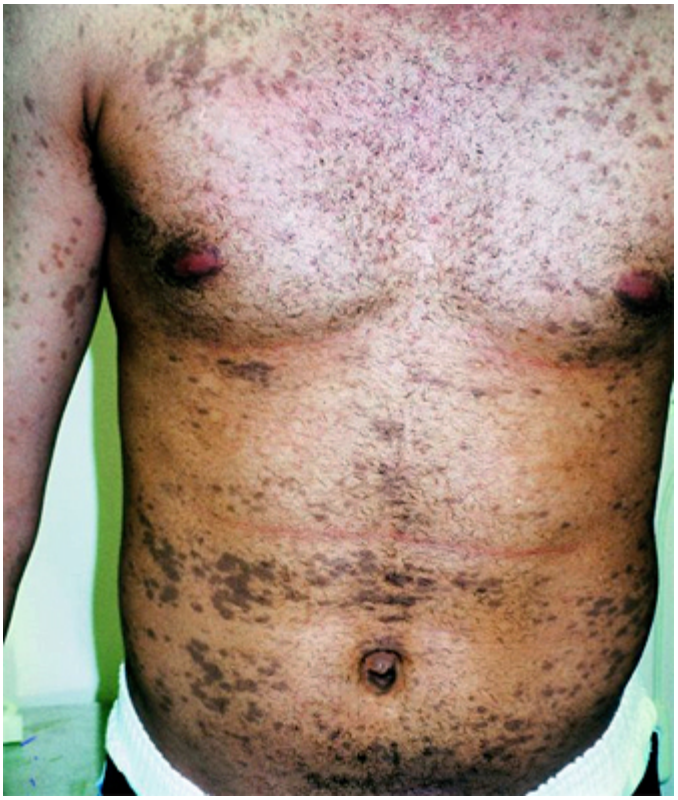


Vesicles and erosions are visible on the dorsum of the hand in a patient with porphyria cutanea tarda related to underlying hepatitis C virus infection.

Courtesy of Jean-François Dufour, MD.

Graphic 74528 Version 1.0

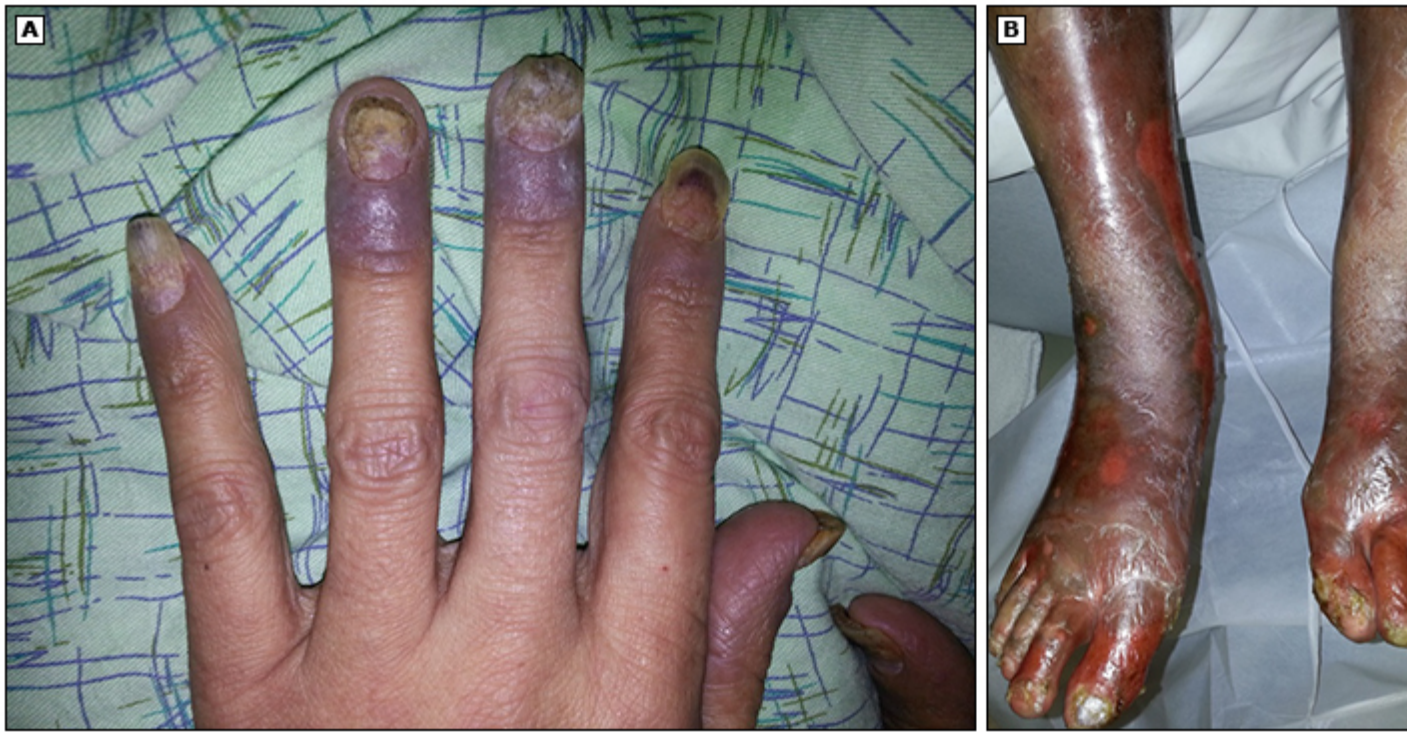
Generalized lichen planus



Violaceous and hyperpigmented polygonal papules are present in a widespread distribution in this patient with generalized lichen planus.

Graphic 50632 Version 1.0

Necrolytic acral erythema



Necrolytic acral erythema is a rare cutaneous disorder associated with hepatitis C virus infection.

(A) Violaceous plaques extend from the distal interphalangeal joint to the fingertips.

(B) Confluent moderately well-defined erythematous to violaceous plaques with superficial erosions on the f and lower legs.

From: Iyengar S, Chang S, Ho B, et al. Necrolytic acral erythema masquerading as cellulitis. Dermatol Online J 2014; 20(11). Reproduc permission.

Graphic 111239 Version 1.0

Contributor Disclosures

Sanjiv Chopra, MD, MACP No relevant financial relationship(s) with ineligible companies to disclose. **Steven Flamm, MD** Grant/Research/Clinical Trial Support: Intercept [Alcohol-related hepatitis]; Madrigal [Fatty liver/NASH]. Consultant/Advisory Boards: AbbVie [Hepatitis C virus]; Gilead [Hepatitis C virus]; Intercept [Primary biliary cholangitis]; Salix [Hepatic encephalopathy]. Speaker's Bureau: AbbVie [Hepatitis C virus]; Gilead [Hepatitis C virus]; Intercept [Primary biliary cholangitis]; Salix [Hepatic encephalopathy]. All of the relevant financial relationships listed have been mitigated. **Adrian M Di Bisceglie, MD** Equity Ownership/Stock Options: Arbutus [Hepatitis B]. Consultant/Advisory Boards: Eiger [Hepatitis D]; HighTide Therapeutics [Primary sclerosing cholangitis, nonalcoholic steatohepatitis]; Ocelot Bio [End stage liver disease]; WCG/ACI [Clinical trial conduct]. All of the relevant financial relationships listed have been mitigated. **Allyson Bloom, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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