

Splenectomy for HIV-Related Immune Thrombocytopenia

Comparison With Results of Splenectomy for Non-HIV Immune Thrombocytopenic Purpura

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Objective: To determine the effectiveness and safety of splenectomy for patients with human immunodeficiency virus (HIV)-related immune thrombocytopenia, using the results of splenectomy for patients with non-HIV immune thrombocytopenic purpura as a control group for comparison.

Design: Retrospective study.

Setting: Tertiary care university hospital.

Patients: Fourteen patients who underwent splenectomy for symptomatic, medically refractory HIV-related immune thrombocytopenia at this hospital from 1988 to 1997. During the same period, 20 patients had splenectomy for treatment of non-HIV immune thrombocytopenic purpura.

Intervention: Splenectomy.

Main Outcome Measures: Platelet response, need for postsplenectomy medical therapy, progression of HIV disease, and complications.

Results: All patients with HIV-related thrombocytopenia had a complete early platelet response to splenec-

tomy, with an elevation of the platelet count to greater than $100 \times 10^9/L$. After a median follow-up of 26.5 months, all but 1 patient had a sustained complete remission with no need for medical therapy for thrombocytopenia. Splenectomy was more effective in the HIV-related thrombocytopenia group than in the non-HIV immune thrombocytopenic purpura group, with significantly higher platelet counts at 1 week and 1 month after splenectomy in the HIV group (t test, $P=.02$ and $P=.009$, respectively). There were significantly fewer patients needing medical therapy for thrombocytopenia after splenectomy in the HIV group (χ^2 test, $P=.02$). There were no remarkable short- or long-term complications in the patients with HIV infection, including no overwhelming postsplenectomy infections. Three patients have died, and 2 patients have developed AIDS since operation.

Conclusions: Splenectomy is effective treatment for patients with symptomatic HIV-related thrombocytopenia that is resistant to medical therapy. The effectiveness of this treatment suggests that the predominant mechanism of thrombocytopenia in HIV-infected patients is increased destruction of platelets because of platelet-associated immunoproteins.

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A SYNDROME of immune thrombocytopenic purpura (ITP) in homosexual men, now recognized to be due to human immunodeficiency virus (HIV) infection, was first reported in 1982 by Morris et al.¹ Similar in many respects to the disease termed either *idiopathic* or *immune thrombocytopenic purpura* in the non-HIV general population, this syndrome has been variously named HIV-related thrombocytopenia, HIV-related (immune) thrombocytopenia, and HIV-associated thrombocytopenia.²

Thrombocytopenia is a common complication of HIV infection, with between 10% and 20% of HIV-infected pa-

tients having a platelet count less than $150 \times 10^9/L$.³⁻⁶ In one large study of HIV-infected patients, 5.3% of patients had severe thrombocytopenia, with a platelet count less than $50 \times 10^9/L$.³ HIV-related thrombocytopenia may develop at any stage of HIV infection; it is not an acquired immunodeficiency syndrome (AIDS)-defining illness, and it occurs in HIV-infected patients from all HIV high-risk groups. Although one study reported a higher prevalence of HIV-related thrombocytopenia in patients with AIDS than in HIV-infected patients without AIDS,⁴ the development of thrombocytopenia is generally thought not to indicate worsened immunodeficiency, and patients with HIV-related thrombocytopenia do not get AIDS

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SUBJECTS AND METHODS

The medical records of all patients who had splenectomy at St Vincent's Hospital between January 1, 1988, and January 1, 1997, were retrospectively reviewed. Before 1988, HIV infectivity was not included on the computer-based record system of admissions to this hospital. Permission to review and report on the medical files of HIV-infected patients was obtained from the New South Wales Department of Health and the National Centre of HIV Epidemiology and Clinical Research. Follow-up information was obtained from the medical records, by postal and telephone inquiry with the patients' local physicians or their hematologists, and with the patients. Follow-up information was available for all patients. Patients were included in the non-HIV ITP group if they had been diagnosed as having ITP and had isolated thrombocytopenia with no clinically apparent associated conditions or other causes of thrombocytopenia.⁹

The following information was recorded for patients who had splenectomy as treatment for either HIV-related thrombocytopenia or non-HIV ITP: age, sex, diagnosis, date of splenectomy, intraoperative and postoperative complications, and length of postoperative stay. All splenectomies were performed through a midline incision. The lowest platelet count before splenectomy, the platelet count 1 week after splenectomy, and any other available platelet counts, were also recorded. End points for recording of postoperative platelet counts were either the last available count or the last count before institution of medical therapy for thrombocytopenia for patients who relapsed or remained severely thrombocytopenic after splenectomy.

For patients who had splenectomy for HIV-related thrombocytopenia, the following additional information was recorded: year of HIV diagnosis, month and year of HIV-related thrombocytopenia diagnosis, risk factors for HIV infection, and stage of HIV disease at the time of operation. Staging was according to the Centers for Disease Control and Prevention (CDC) 1993 revised classification,³¹ in which group 1 is acute HIV syndrome (seroconversion illness), group 2 is asymptomatic infection, and group 3 is progressive generalized lymphadenopathy. Group 4 is AIDS, defined by the CDC case definitions for AIDS, and including in the revised classification all HIV-infected persons who have less than $0.20 \times 10^9/L$ CD4⁺ T lymphocytes (200/ μ L), or a CD4⁺ T lymphocyte percentage of total lymphocytes of less than 14. The CD4⁺ count measured closest to operation was recorded for each patient, provided that the cell count was measured within 3 months of operation.

Symptoms and signs of thrombocytopenia were recorded for the HIV-related thrombocytopenia group, as were the details of medical treatment for thrombocytopenia. Only medications given for thrombocytopenia more than 3 months after splenectomy were recorded, to avoid recording the use of drugs that were being gradually weaned after operation. Also noted were the results of histopathological examination of the spleen, and whether vaccines for encapsulated organisms were given. Follow-up information recorded included whether there had been progression of HIV disease, and whether any severe or overwhelming infections had occurred.

Variables for the 2 groups who underwent splenectomy for HIV-related thrombocytopenia or for non-HIV ITP were compared using the Student *t* test and the χ^2 test.

sooner than others.³ Spontaneous remission may occur in up to 20% of cases,^{5,7} and splenectomy is only required for the minority of patients who have severe, symptomatic, medically resistant thrombocytopenia.

There are many similarities between classic ITP in non-HIV infected individuals and HIV-related thrombocytopenia. Clinical features for both conditions, if present, are the same. These include spontaneous or easy bruising or bleeding, petechiae, gastrointestinal tract hemorrhage, and (uncommonly) intracranial hemorrhage. A rise in the platelet count after administration of corticosteroids and intravenous immunoglobulin is usually observed in both conditions, although this rise is often not sustained after withdrawal of the drugs. Splenectomy is effective long-term therapy for patients with classic chronic ITP,^{8,9} and despite concerns that splenectomy in HIV-infected patients might increase the risk of developing AIDS¹⁰ or overwhelming postsplenectomy sepsis, splenectomy has been successfully used for the treatment of HIV-related thrombocytopenia.^{2,11-17}

Other similarities between ITP and HIV-related thrombocytopenia include the finding of increased titers of antiplatelet antibodies in both conditions, suggesting that in HIV-related thrombocytopenia, as in classic ITP, increased removal of antibody-labeled (opsonized) platelets is a fundamental mechanism of the thrombocytopenia.^{15,16,18} Normal or increased numbers of mega-

karyocytes are seen in the bone marrow in both conditions, and the spleen is typically of normal size in both conditions.¹⁹

There are differences between the 2 diseases, however. Classic ITP, unlike HIV disease in this society, more commonly affects women, and spontaneous remission may be more common in HIV-related thrombocytopenia. Antiretroviral nucleoside analog drugs such as zidovudine (AZT) may be helpful in the treatment of HIV-related thrombocytopenia but are not used for patients with non-HIV ITP. Unlike classic primary ITP, but similar to secondary ITP that follows a viral infection or drug reaction, immune complexes may be more important than antiplatelet antibodies in the pathophysiology of HIV-related thrombocytopenia.^{20,21} There is also evidence that defective production of platelets, rather than just increased destruction of platelets as in ITP, is occurring in at least some cases of HIV-related thrombocytopenia.²²⁻²⁶ The production defect is at the megakaryocyte level, perhaps due to infection of the megakaryocyte by the HIV virus itself.^{27,28}

St Vincent's Hospital is located within an area of Sydney, Australia, with a high concentration of HIV-infected individuals. The age-standardized average annual incidence of AIDS in this area is 39.6 per 100 000 population, the highest rate in Australia.²⁹ During the first 7 years of this study, 1502 patients with AIDS were ad-

mitted to St Vincent's General Hospital, equivalent to 26.8% of known AIDS cases in Australia up to that time.³⁰

This study was undertaken to determine the effectiveness and safety of splenectomy for patients with HIV-related thrombocytopenia, using the results for patients who underwent splenectomy for non-HIV ITP during the same period as a control group for comparison. We know of no report of a similar comparative study.

RESULTS

Eighteen (17%) of the total 106 patients who had splenectomy at this hospital in the 9-year period from January 1988 to January 1997 were infected with HIV. Splenectomy was the fourth commonest operation performed on HIV-infected patients during this period, after anorectal operations,³² vascular access procedures, and appendectomies. Four of the 18 HIV-infected patients underwent splenectomy for diseases other than HIV-related thrombocytopenia, and will not be discussed further.

Fourteen patients had splenectomy for HIV-related thrombocytopenia at this hospital during the period reviewed. All were men. The median age of this group was 32 years (range, 21-57 years). HIV risk factors were homosexuality (12 patients) and blood transfusion (2 patients). At the time of splenectomy, 6 patients had AIDS (CDC group 4), and 8 patients were classified as CDC group 2 (asymptomatic infection; HIV-related thrombocytopenia is not an AIDS-defining illness). HIV-related thrombocytopenia was diagnosed a median 4 years after diagnosis of HIV infection, and splenectomy was performed a median 12 months after diagnosis of HIV-related thrombocytopenia (range, 1-49 months). Median lowest preoperative serum platelet count was $8 \times 10^9/L$ (range, $2-22 \times 10^9/L$), and all patients had symptoms of thrombocytopenia, which included spontaneous or easy bruising (11 patients), spontaneous or easy bleeding (8 patients), and gastrointestinal tract hemorrhage (3 patients). Bone marrow aspirates were performed in 8 patients and showed a hypercellular marrow in 4 patients, and a normal marrow in 4 patients.

All patients in this group had thrombocytopenia that was refractory to medical treatment. All patients received at least 1 course of intravenous immunoglobulin as treatment for immune thrombocytopenia, and all but 1 patient, who had suffered recurrent severe infections, received corticosteroid therapy for at least 1 month. Corticosteroid doses ranged from 10 to 60 mg/d. Four patients were also given zidovudine (1 g/d), 3 patients received danazol (400 $\mu\text{g}/\text{kg}$ for 5 days), and 1 patient received vincristine sulfate. These medical therapies failed to induce a long-lasting rise in the platelet count. The indications for splenectomy in these patients were thus a combination of symptomatic thrombocytopenia and failed medical therapy.

At operation, median CD4 cell count was $0.365 \times 10^9/L$ (range, $129-570 \times 10^9/L$). Pneumococcal vaccine was given perioperatively in every case, and 2 patients received vaccine for meningococcus and *Haemophilus*. There were no significant intraoperative complications, including no bleeding problems. Median spleen weight was 246 g

(range, 140-540 g). One accessory spleen was found. Histopathological examination showed congestion of the red pulp in 7 cases, with or without follicular hyperplasia of the white pulp in 4 cases, and a normal spleen in 5 cases.

There was no operative mortality. Postoperative complications were recorded for 6 patients, consisting of pulmonary atelectasis in 5 patients, wound infection in 2 patients (1 deep wound infection requiring reopening and dressing of the wound, 1 superficial infection requiring antibiotics only), and urinary retention in 1 patient. Median postoperative stay was 8 days, with a range of 6 to 23 days. After a median follow-up of 26.5 months (range, 14-86 months), 3 patients have died of AIDS-related diseases that were unrelated to their thrombocytopenia or splenectomy, and 3 previously CDC group 2 patients have developed AIDS. The remaining 9 patients are alive and have not developed AIDS if they did not have AIDS at operation. Four patients were prescribed lifelong penicillin prophylaxis, and no patient has had an opportunistic infection related to their postsplenectomy state.

All patients with HIV-related thrombocytopenia had an initial complete response to splenectomy (defined here as an increase in platelet count to $>100 \times 10^9/L$),¹⁵ and the sustained complete remission rate was 93% over a median follow-up of 26.5 months. Only 1 patient, a 57-year-old man with transfusion-acquired HIV infection and a CD4 count at splenectomy of $0.129 \times 10^9/L$, needed to recommence medical therapy for recurrent symptomatic thrombocytopenia (at 9 months after splenectomy).

The patients who had splenectomy for HIV-related thrombocytopenia were compared with those who had splenectomy for non-HIV ITP (**Table**). During the 9-year study period, 20 patients had splenectomy for treatment of ITP. Unlike the exclusively male HIV-related thrombocytopenia group, the patients with ITP were mostly women, but the 2 groups were not significantly different with respect to age, duration of postoperative stay, or the numbers of patients with postoperative complications (Table). Ten of the 20 patients in this group suffered some morbidity after splenectomy, 1 of whom died. The morbidity comprised pulmonary atelectasis in 7 patients, left lower lobe collapse in 1 patient, septicemia and septic arthritis due to an infected intravenous long line in 1 patient, and a superficial wound infection in 1 patient. A 78-year-old man with a history of ischemic heart disease died suddenly due to acute myocardial infarction on postoperative day 8. An accessory spleen was not identified at operation in any of the patients in this group.

The early response to splenectomy was better in the HIV-related thrombocytopenia group, with a significantly higher median platelet count in that group at 7 days and 30 days after operation (Table). Significantly more patients in the ITP group than in the HIV-related thrombocytopenia group relapsed or never benefited from splenectomy, as shown by the numbers of patients in each group who needed medical therapy for thrombocytopenia more than 3 months after splenectomy (Table). This finding is more meaningful than that obtained by comparing the platelet counts of patients in each group at later intervals after splenectomy, because if medical therapy for thrombocytopenia was required for a patient, no fur-

Comparison of HIV-Related Thrombocytopenia Group With Non-HIV Immune Thrombocytopenic Purpura Group*

Variable	HIV-Related Thrombocytopenia (n=14)	Non-HIV ITP (n=20)	Test Statistic	P
M/F ratio	14:0	8:12	$\chi^2=13.0$	<.001
Median age, y (range)	32 (21-57)	35.5 (17-80)	$t=0.95$.35
Median postoperative stay, d (range)	8 (6-23)	10 (3-30)	$t=0.19$.85
No. of patients with postoperative complications	6	10	$\chi^2=0.2$.66
No. of patients receiving medical therapy for thrombocytopenia after splenectomy	1	9	$\chi^2=5.7$.02
Median platelet count, $\times 10^9/L$ (range)				
Lowest presplenectomy	8 (2-22)	7 (2-172)	$t=0.70$.49
At day 7, postsplenectomy	547 (177-970)	440 (9-808)	$t=2.39$.02
At day 30, postsplenectomy	346	80	$t=3.11$.009

*HIV indicates human immunodeficiency virus; ITP, immune thrombocytopenic purpura.

ther platelet counts were recorded for that patient. A comparison of platelet counts measured more than 3 months after splenectomy thus involves only patients in each group who have received continued benefit from the operation, and there was no significant difference between the platelet counts in these selected patients in the HIV and non-HIV groups 1 month after splenectomy (probability values for this comparison: days 60-90, $P=.42$; days 120-210, $P=.55$; days 240-390, $P=.89$; days 420-600, $P=.72$; days 630-960, $P=.93$; and day 1020+, $P=.09$; all Student t test).

COMMENT

This study demonstrates that splenectomy is effective treatment for patients with symptomatic HIV-related thrombocytopenia that is resistant to medical therapy. All patients with HIV-related thrombocytopenia in this study had a complete early platelet response to splenectomy, with an elevation of the platelet count to above $100 \times 10^9/L$, and 93% of patients had a sustained complete remission after a median follow-up of 26.5 months.

The excellent results for splenectomy for HIV-related thrombocytopenia in this study are similar to those of other studies.^{2,11-17} Combining the results for the 8 largest previously published series^{2,11-17} shows that splenectomy provided an early elevation of the platelet count to above $100 \times 10^9/L$ in 127 (91%) of the total 140 patients in those series, and an elevation to above $50 \times 10^9/L$ in another 3% of patients. Two previously published series have detailed long-term follow-up information.^{15,16} After a mean follow-up of 70 months in the largest series, only 8 (12%) of 68 patients had relapsed,¹⁵ while only 3 of 30 patients had platelets less than $50 \times 10^9/L$ after a mean of 42 months after splenectomy in the other large study.¹⁶

Splenectomy is effective treatment for classic chronic ITP in the non-HIV general population, and is indicated in cases of severe thrombocytopenia that have been refractory to medical therapy for some time.^{8,9} Most studies suggest that splenectomy provides a sustained correction of the platelet count to normal levels, with no requirement for medical therapy, in approximately two thirds of patients with ITP.⁹ This study compared the results of splenectomy for patients with HIV-related thrombocytopenia with the results of splenectomy for pa-

tients with non-HIV ITP. During the period examined, splenectomy was more beneficial for the HIV-related thrombocytopenia group, who had significantly higher early postsplenectomy platelet counts, and significantly more of whom remained in remission after splenectomy. It is not possible to conclude on the basis of this study that splenectomy is generally more effective for treatment of HIV-related thrombocytopenia than for treatment of non-HIV ITP. There are insufficient numbers of patients in this study for such a statement, and it should also be noted that the results for the patients with non-HIV ITP were not as good as in other studies.^{8,9} There was no significant difference between the HIV-infected and the HIV-noninfected groups for the variables age, complication rate, or length of postoperative stay. As expected, there was a predominance of males in the HIV group, while there were more females in the non-HIV ITP group.

Splenectomy is effective in thrombocytopenic conditions such as classic ITP, which are caused by increased platelet destruction because the spleen is the major site of destruction of opsonized platelets, and because antiplatelet antibodies, if present, may be manufactured in the spleen. Several platelet kinetics studies, which use indium 111-labeled autologous platelets to calculate platelet survival and production, have found that impaired platelet production, as well as increased destruction, is present in some HIV-infected patients with thrombocytopenia.²²⁻²⁶ The overall effectiveness of splenectomy as treatment for thrombocytopenia related to HIV infection suggests that increased destruction of platelets because of platelet-associated immunoproteins (antibodies, immune complexes, or both) is the predominant mechanism of thrombocytopenia in HIV-infected patients.

The authors of one platelet kinetics study have suggested that the mechanism of thrombocytopenia might be different at earlier and later stages of HIV infection.²² These authors found that more recently HIV-infected patients were more likely to have increased destruction as the mechanism of thrombocytopenia, and were therefore more likely to benefit from splenectomy, whereas patients with AIDS were more likely to have decreased platelet production as the predominant mechanism, with less benefit from splenectomy. The authors commented, however, that their results had a wide variabil-

ity, and that the mechanism of thrombocytopenia was not invariably related to the stage of HIV disease. There are insufficient numbers of patients with AIDS among the patients who have undergone splenectomy for HIV-related thrombocytopenia in published series to adequately test this suggestion. Only 3 of the 8 previously published series referred to above included any patients with AIDS. Including the 6 patients with AIDS in this study, specific information is available for only 11, of whom 7 patients (64%) had an early postsplenectomy complete response, with a platelet count elevated to more than $100 \times 10^9/L$. Three patients with AIDS (27%) had an early partial response, and 1 patient had no response. Long-term follow-up information for patients with AIDS is only available for the 6 patients in this present study. At a median follow-up of 25.5 months (range, 14-70 months), 5 of the 6 patients with AIDS are receiving no medical treatment for thrombocytopenia, with a platelet count greater than $150 \times 10^9/L$. Only 1 patient has relapsed, requiring recommencement of medical therapy at 7 months after splenectomy. These patient numbers are too small to allow any conclusions to be made, but they indicate that the published early results for splenectomy for HIV-related thrombocytopenia in patients with AIDS have not been as good as those for HIV-infected patients without AIDS, although a majority of patients with AIDS have nevertheless benefited from the operation. Further studies investigating the relationship between effectiveness of splenectomy and HIV stage, CD4 count, and perhaps HIV viral load, are required.

Splenectomy seems to be a safe procedure in HIV-infected patients. Operative morbidity and mortality of splenectomy for HIV-related thrombocytopenia in published series are comparable with the less than 1% mortality and approximately 1% major hemorrhage rates historically reported for splenectomy for classic non-HIV ITP.⁹ Earlier fears that splenectomy might enhance progression to AIDS in HIV-infected patients¹⁰ have not been supported by published series.^{12,14,15,33} The findings of this present study, in which 3 patients progressed from asymptomatic infection to AIDS after being infected with HIV for 2, 6, and 11 years, are unremarkable in this regard. Oskenhendler et al¹⁵ found, using a Cox regression model, that splenectomy had no influence on survival, AIDS-free survival, or AIDS progression rate in patients with HIV-related thrombocytopenia.

Although no patient in this series developed severe or overwhelming postsplenectomy infection, other authors have reported this complication in HIV-infected patients who underwent splenectomy.^{15,34} HIV infection itself has been reported to greatly increase the risk of infection with the pneumococcus and other encapsulated organisms, which are the likely infecting organisms in cases of overwhelming postsplenectomy infection,^{35,36} and the activity of tuftsin, an endogenous tetrapeptide that stimulates phagocytosis and is released from the Fc fragment of IgG by a splenic endocarboxypeptidase, is reduced in both splenectomized patients and patients with AIDS.³⁷ It is thus likely that patients who have both HIV infection and previous splenectomy are at greater risk of overwhelming postsplenectomy infection than patients with non-HIV splenectomy.

Severe pneumococcal infections have been recorded in HIV-infected patients with splenectomy who were administered pneumococcal polyvalent vaccine before splenectomy.^{34,36} Although one report found that patients with HIV-related persistent generalized lymphadenopathy may fail to produce a normal anti-pneumococcal antibody response,³⁸ another study showed that HIV-infected individuals respond to pneumococcal immunization with adequate antibody titers,³⁹ and most authors recommend giving pneumococcal vaccine to these patients.^{2,13,15-17} The vaccine is preferably given at least 2 weeks before elective splenectomy, following the recommendations of the CDC Advisory Committee on Immunization Practices.⁴⁰ Vaccination for *Haemophilus* and meningococcus and lifelong penicillin prophylaxis are now also recommended for this group of patients at our hospital.

Splenectomy is effective long-term treatment for most patients with symptomatic, medically refractory thrombocytopenia due to HIV-related thrombocytopenia. As more is learned regarding the mechanism of thrombocytopenia in HIV infection, a more sophisticated selection process for splenectomy in these patients may become appropriate.

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Porphyrin Abnormalities in Acquired Immunodeficiency Syndrome

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Objective: To examine prospectively porphyrin metabolism in a human immunodeficiency virus (HIV)-positive population.

Setting: Specialist referral unit at the Department of Genitourinary Medicine, St James's Hospital, Dublin, Ireland.

Patients: Twenty-eight men and 5 women (age range, 18-35 years). Twenty-nine were current or previous intravenous drug abusers. Four were thought to have sexually acquired HIV infection. All had a history of acquired immunodeficiency syndrome-defining illnesses. The patients were selected as a consecutive sample from the inpatient department. Eligibility criteria were cooperation with urine and stool collection and confirmed HIV seropositivity. The patients were matched to 2 groups: 1 with normal results of porphyrin studies and the other with abnormal findings from porphyrin studies.

Intervention: None.

Main Outcome Measures: Plasma, urine, and stool porphyrin excretion patterns.

Results: Of the 33 patients in the study, 13 (40%) had increased urinary porphyrin excretion. All but 2 of these patients were seropositive for hepatitis C virus. No study patient had clinical evidence of porphyria. Four patients (12%), however, had urine and stool porphyrin excretion patterns that were classic for porphyria cutanea tarda. All 4 of these patients were hepatitis C virus-positive. Patients with porphyrinuria had a greater degree of immunosuppression ($P=.002$) than those with normal porphyrin metabolism, and they were more likely to be taking zidovudine ($P=.009$).

Conclusions: Commonly, porphyrin metabolism is abnormal in persons with established HIV infection. Hepatitis C may contribute to abnormal porphyrin metabolism. An unexpected number of patients studied had porphyrin excretion patterns that were characteristic of porphyria cutanea tarda, and all of these were hepatitis C virus-positive. A diagnosis of porphyria cutanea tarda, especially in a young patient, should prompt investigation for underlying HIV and hepatitis C virus infections. Dermatologists should be aware of the infectious risk associated with the vesicles and erosions in these patients. Porphyrin studies should be performed in any patient with HIV and photosensitivity. *Arch Dermatol*. 1996;132:1443-1447

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