

Letters to the Editor

Successful Treatment of Hepatitis B–Associated Vasculitis With Lamivudine

To the Editor:

Vasculitis is perhaps the most serious extrahepatic manifestation of hepatitis B virus (HBV) infection.^{1,2} Treatment with corticosteroids and immunosuppressive agents may worsen the hepatic disease because of enhanced viral replication.³ We report a case of HBV-associated leukocytoclastic vasculitis that responded to lamivudine treatment.

A 59-year-old woman with a history of leukocytoclastic vasculitis was referred in 1998 for evaluation of hepatitis B. She complained of fatigue and recurrent flares of skin vasculitis associated with soft tissue swelling for the past 20 years, which had responded to variable doses of prednisone. She had been taking prednisone (5–10 to 30 mg/d). In 1978, she was hospitalized for evaluation of a petechial, nonpruritic, body-wide rash. Biopsy of the lesion showed leukocytoclastic vasculitis. She was HBsAg positive. In 1998, she had no hepatosplenomegaly or stigmata of chronic liver disease. At this time, she was HBsAg and anti-HBc positive, anti-HBs negative, HBeAg negative, and anti-HBe positive. The quantitative serum HBV DNA level was 9.3 pg/mL. Polymerase chain reaction analysis for both serum anti-HCV and HCV RNA was negative; analysis for cryoglobulins was positive.

Treatment with lamivudine (150 mg/d) was started. One month later, the serum HBV DNA level was undetectable, and her vasculitis was less intense. Over the next 7 months, the prednisone dose was gradually tapered, and this therapy was eventually stopped. Twenty-one months later, her vasculitic lesions had completely resolved. Her lamivudine dosage was reduced to the standard (100 mg/d). At present, her HBV DNA level is undetectable. She has not taken any immunosuppressive agents for the last 3 years, and she continues to receive oral lamivudine therapy.

In the absence of treatment of HBV infection, the historic treatment of hepatitis B–associated vasculitis consisted essentially of immunosuppressive agents. Corticosteroids, once a form of treatment of hepatitis B–associated vasculitis, were subsequently shown to enhance HBV replication. Thus, steroid-induced immunosuppression actually lowers the frequency of viral seroconversion.³

The recent availability of lamivudine as a direct anti-HBV agent has now opened new treatment options. Lamivudine in combination with various immunosuppressive regimens aids in the successful management of HBV–associated polyarteritis nodosa. Lamivudine was added to regimens containing cyclophosphamide with prednisone,⁴

interferon- α with prednisolone,⁵ interferon- α and prednisone with plasma exchange,⁶ and prednisone with plasmapheresis.⁷ To our knowledge, however, there are no previous reports of treatment of HBV-associated vasculitis with lamivudine as a single agent.

The prospect of treating viral hepatitis-associated immunologic syndromes with antivirals and not immune suppressants is an attractive option. Shapiro et al.⁸ successfully used injectable interferon- α in the treatment of HBV-associated glomerulonephritis with remission of nephrotic syndrome. Early detection of a viral etiology of a vasculitic syndrome may lead to specific antiviral therapy rather than treatment with nonspecific and toxic immunosuppressive agents. In the case of lamivudine, sustained and durable HBV eradication appears to be elusive, and end points are not well defined. In the case described herein, the patient had very low circulating levels of HBV DNA, yet this seemingly low level of viremia resulted in significant vasculitis. In addition, at the time of presentation in 1998, she was HBeAg negative.

The present case thus illustrates that following effective viral suppression with lamivudine, corticosteroids may be successfully weaned and terminated in the treatment of HBV-associated vasculitis. This case also suggests that early introduction of lamivudine in the treatment of HBV-associated vasculitis may prevent morbidity and mortality associated with both this condition and immunosuppressive therapy.

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Synchronous Nonfunctioning Neuroendocrine Carcinoma of the Pancreas and Appendix

To the Editor:

We report the rare case of a female patient with a non-functioning neuroendocrine pancreatic carcinoma and a simultaneously and independently growing carcinoid tumor of the appendix. Although lymph node and liver metastases were present, extended multivisceral resection was performed.

A 47-year-old female patient underwent laparotomy under the suspicion of pancreatic cancer. At operation, the tumor was found to grow within the pancreatic tail. Liver metastasis was detected and atypically completely resected. No tumor-suspicious lesions were seen in the pancreatic corpus or head. Further exploration revealed an additional tumor mass that developed out of the cecum, growing within the mesentery of the small bowel and the right colon toward the lower margin of the pancreas. Multiple enlarged lymph nodes were found around the large blood vessels. Since intraoperative frozen-section diagnosis was not able to differentiate between a low-malignant pancreatic tumor and a pancreatic carcinoma, multivisceral resection including splenectomy, atypical liver resection, and resection of the pancreatic tail and the right hemicolon was performed (R0). The patient was discharged from the hospital symptom free on day 14 after surgery. Six months after discharge, the patient had gained weight and was free of any abdominal symptoms. Restaging, including somatostatin receptor scanning, showed no evidence of tumor recurrence or metastasis.

Independently growing synchronous metastatic neuroendocrine carcinoma of the pancreas (pT3 N2 M1[hep]) and appendix (pT2 N2 Mx). The tumor cells were strongly positive for chromogranin A with a rare mitotic action. The expression for serotonin and synaptophysin was positive. Negative immunostaining was found for gastrin, α_1 -antitrypsin, and insulin with positive internal control for insulin in normal pancreatic tissue.

The patient had the extremely rare diagnosis of a well-differentiated neuroendocrine carcinoma of the pancreas and a synchronously growing carcinoid tumor of the appendix. In contrast to acinous pancreatic carcinoma, the 5-year survival rate for patients with nonfunctioning neuroendocrine pancreatic carcinoma is between 40% and 50%.¹ After curative resection, the 5-year survival even rises up to 75%, while noncurative resection is associated with a 5-year survival rate of 30%–40%. Because of the young age of the patient, the small amount of liver metastasis, and the resectable tumor masses, we believed that she would benefit in terms of survival from this extensive surgical procedure, which was performed.

Pancreatic islet cell tumors with cytologic and immunohistochemical characteristics of functioning neuroendocrine tumors are classified as nonfunctioning neuroendocrine tumors if the patient lacks the clinical aspects of a specific neuroendocrine syndrome and does not, as our patient, have elevated serum gastrointestinal hormone levels.² According to the literature, the annual incidence of neuroendocrine pancreatic carcinoma is 0.5 to 1 case per 100,000 population.³ Twenty percent to 30% of these carcinomas are nonfunctioning, present during the sixth decade of life, occur in the head of the pancreas, and are associated with a 5-year survival rate of $\approx$ 50% following resection.⁴

Carcinoid tumors of the appendix are almost always found accidentally during surgery for suspected appendicitis.⁵ The prevalence of carcinoid tumors after appendectomy is 0.69%.⁶ They comprise 18.9% of all carcinoid tumors and 25.7% of all gastrointestinal carcinoids.⁵ The frequency of metastasis from these tumors has been reported between 1.4% and 8.8% in different series^{7,8} and rises with the size of the tumor.⁹ Because most of the appendix carcinoids are <2 cm in size and have no metastasis, the 5-year survival rate is reported to be 90%–100%.¹⁰ To our knowledge, there is no report of two independently growing neuroendocrine carcinomas in the literature, although multifocal growth is well described.

The central point of interest of this case is the site of the primary tumor, since two large tumor foci were detectable within the pancreas and the appendix. The suspicion of two similar and synchronous but independently growing tumors is the most probable, since lymphovascular invasion and metastasis of a primary pancreatic carcinoma into the appendiceal region are as unlikely as metastasis of a primary appendiceal carcinoid into the pancreas.

In conclusion, patients with neuroendocrine pancreatic carcinoma seem to benefit from multivisceral resections since their prognosis is much better than of those with adenocarcinoma of the pancreas. As long as frozen-section diagnosis is not able to differentiate between neuroendocrine carcinoma and adenocarcinoma, extended resections should be performed.

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Complementary Medicine in Gastroenterology: More Than a Fad?

To the Editor:

Complementary medicine (CM) is “diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine,”¹ a definition now adopted by the Cochrane Collaboration. CM has become important, not least through its increasing popularity with our patients. Among the U.S. general population, for instance, the 1-year prevalence of CM use rose from 33% in 1990 to 42% in 1997.² Many patients use CM for gastroenterological conditions like irritable bowel syndrome, constipation, intestinal cancer, etc. We recently evaluated seven popular CM books with a view of defining which treatments were advised for which conditions.³ Among indications relevant for gastroenterologists, two featured prominently²: cancer (133 different CM treatments recommended) and irritable bowel syndrome (69 different treatments recommended). There was very little agreement between the authors of these books, and everything seemed to be deemed useful for anything. In a similar investigation, we asked 223 professional CM organizations for which indications their treatment might be helpful.⁴ The following CM treatments were recommended for irritable bowel syndrome: Bowen technique, chiropractic, hypnotherapy, massage, and reflexology. Yet, positive evidence for efficacy exists only for hypnotherapy (see below).

Several CM treatments have been tested for overweight. The results are negative for acupuncture⁵ and guar gum.⁶ A meta-analysis of chitosan for weight reduction included five randomized, controlled trials with a total of 386 subjects.⁷ It demonstrated a statistically significant effect on body weight, but various methodological limitations precluded

firm conclusions about the effectiveness of chitosan. Another meta-analysis included 10 randomized, controlled trials of chromium picolinate for body weight reduction.⁸ The overall effect was statistically superior to placebo, but the effect size was too small to be clinically relevant. In other words, no CM therapy has so far been shown to be convincingly useful for weight reduction. This is in stark contrast to the money that is being made by manufacturers promising the opposite.

Although much of CM seems to have the characteristics of a fad, there are also some areas where encouraging evidence has recently emerged. A few examples might substantiate this statement. At least four randomized, controlled trials with adult patients and three randomized, controlled trials with pediatric patients yielded overall positive evidence for biofeedback as a treatment of chronic constipation.³ For the same indication, there is some encouraging trial evidence for the herbal remedy aloe vera and for abdominal massage therapy.³ Acupuncture and reflexology have also been tested in clinical trials for this condition but have not shown any promise.³ Patients with irritable bowel syndrome can be helped by treatments such as hypnotherapy,³ peppermint oil,⁹ or isphagula.³ Several studies have demonstrated nausea and vomiting of various etiologies can be relieved by acupuncture,¹⁰ ginger,³ or hypnotherapy.³

These examples imply that at least some forms of CM are worthy of consideration for clinical use or further research. It seems obvious that each therapy must be evaluated on its own merit. Such evaluations also need to consider potential risks of CM.¹¹ In particular, herbal medicines can be hepatotoxic,¹¹ contaminated with heavy metals, or adulterated with synthetic drugs.¹² Many also have the potential to interact with prescribed medicines.³ Whenever CM is used as an alternative to conventional medicine, even seemingly harmless treatments (e.g., homeopathic remedies) can become positively life threatening.³ One important step in the right direction would thus be to abandon the term “alternative” altogether.

The take home message for gastroenterologists seems simple: not all CM is a useless fad; some therapies have shown considerable promise, but most have so far not been investigated systematically. To define which form of CM does more good than harm, we need more and better quality research into this complex area. Because so many of our patients use CM, this would seem to be a matter of some urgency.

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Chronic Autoreactive Urticaria in a Patient with Ulcerative Colitis

To the Editor:

Chronic urticaria (CU) is now recognized as an autoreactive disorder in a substantial fraction of patients. Autologous serum skin testing (ASST) reveals a wheal and flare reaction in up to 60% of patients, which indicates the presence of circulating histamine-releasing factors. The serological mediator of wheals has been demonstrated to be an autoantibody directed either to the high-affinity IgE receptor (FcεRI) in ≈25% of cases or to IgE in ≈5% of cases.^{1,2} In the remaining patients with positive ASST, a hitherto undefined histamine-releasing factor causes dermal mast cell degranulation.³ The autoimmune basis of many cases of CU is reinforced by the association with other autoimmune disorders, namely, autoimmune thyroiditis.⁴ Ulcerative colitis (UC) is characterized by an abnormal immune response to dietary or microbial antigens found in the intestinal lumen and by intrinsic alterations in mucosal barrier function.⁵ T cell hyperactivation, development of self-reactive B cells, and production of autoantibodies such as perinuclear antineutrophil cytoplasmic antibodies and antitropomyosin antibodies demonstrate that in many UC patients the immune response is skewed toward autoimmunity.⁶ In addition, the development of autoantibodies to various autoantigens may contribute to immune-mediated injury at extracolonic sites. UC is associated with other autoimmune disorders, such as erythema nodosum, hyperthyroidism,⁷ autoimmune thyroiditis, and primary sclerosing cholangitis; however, an association with CU has not been established. So far, only one case of CU in a 17-year-old patient with a

history of UC has been reported.⁸ We describe the occurrence of ASST-positive CU in a patient with UC.

A 44-year-old woman presented to our outpatient clinic because of urticaria lasting ≈1 year. Her history revealed the onset of UC at the age of 31 years; she was first treated with sulfasalazine and then with mesalazine and prednisone. Erythema nodosum occurred when she was 37 years old. In the last few months, she had a relapse of UC with prominent rectal involvement. Current treatment was sulfasalazine and mesalazine enema. Urticaria had started ≈3 months before UC reactivation. There was no relation between drug or food ingestion and urticaria exacerbation. The patient was taking an H₁ antihistamine (mizolastine, 10 mg/d) as needed, and urticarial symptoms were controlled satisfactorily. However, urticaria relapsed after every attempt to interrupt antihistamine therapy.

Results of physical examination were normal, as were blood tests, including inflammatory tests, hemocytometric tests, and liver, kidney, and thyroid function tests. Antinuclear autoantibodies were absent, and levels of complement factors C3 and C4 were in the normal range; analysis of stool was negative for *Helicobacter pylori* and parasites. Skin prick tests for food allergens revealed a weak positivity for tomato, but no relation was reported between tomato ingestion and urticaria exacerbation. Furthermore, determination of specific IgE for most common food allergens by UniCAP (Pharmacia, Uppsala, Sweden) was negative. ASST was performed according to the method of Sabroe et al.⁹ Intradermal injection of 50 μL of autologous serum caused a wheal (1 × 1.2 cm) and flare (4 × 4 cm) reaction peaking within 30 minutes and subsiding within 1 hour. Intradermal injection of 50 μL of saline solution did not provoke any wheal and flare reaction (negative control), whereas a normal reactivity was observed after skin prick test with 10 mg of histamine/mL (positive control).

ASST is a screening test for histamine-releasing autoantibodies,⁹ and its positivity indicates that the patient had autoreactive CU. Occurrence of ASST-positive CU in a patient with UC may be more than a mere coincidence, and an association between the two disorders may be hypothesized. Both diseases might share an immune abnormality consisting of T cell hyperactivation and development of autoantibody-producing self-reactive B cells. It is also of interest that CU antedated the UC relapse, thus signalling disease reactivation as sometimes happens with other extraintestinal manifestations of UC.

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