pannicolau testing sooner than recommended by guidelines, especially after normal co-testing results. A novel benefit of co-testing is the ability to extend screening intervals immediately among women who have no prior screening or whose screening history is unavailable if both test results are normal; yet, the lowest adherence to guidelines was for the vignette of a woman with unknown Papanicolaou test history and negative co-test results (3.1%, all years combined). The finding of exceedingly low adherence in this scenario is troubling because reports from a large US cohort demonstrate that more than 90% of women will have normal co-testing results. The highest adherence to guidelines occurred when the recommended interval was less than 3 years, suggesting that clinicians are willing to adhere to guidelines if more vigilant testing is recommended. The ability to obtain prior screening results and the use of electronic medical records or systems changes, such as office reminders or reimbursement packages, may help achieve adherence to recommended intervals.

The low response rate in 2007 (NAMCS) was a limitation of our study. However, estimates were weighted to physician population and accounted for survey nonresponse. Uncertain concordance of practitioner response to hypothetical vignette with actual practice might also be of concern. Vignettes, however, have been shown to be inexpensive and useful tools for measuring quality of care by physicians. Important strengths are the inclusion of the latest NAMCS and NHAMCS data available and the consistent methodology, which make the survey a useful tool to gauge changes in clinicians’ recommendations over time. Future analyses will monitor adherence to newer guidelines that recommend extending screening intervals to 5 years among women with normal co-testing results, a strategy designed to achieve a reasonable balance between benefits and harms.

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Rituximab is a chimeric monoclonal antibody that targets CD20 antigens on B cells. It has been approved by the US Food and Drug Administration for the treatment of B-cell non-Hodgkin lymphoma and rheumatoid arthritis that is refractory to treatment with anti–tumor necrosis factor. Rituximab induces B-cell depletion and influences T-cell immunity, which could consequently predispose patients to serious infectious complications. Herein we describe the reactivation of cerebral toxoplasmosis after rituximab therapy in a patient with cutaneous vasculitis associated with type I cryoglobulinemia.

See Invited Commentary at end of letter

Report of a Case. A 71-year-old woman presented with cutaneous ulcerations on her legs. The patient was not taking any medications and had no history of infections. A biopsy of the skin lesions revealed small-vessel neutrophilic vasculitis, and direct immunofluorescence revealed vascular IgM deposits. Serum protein electrophoresis revealed IgM κ monoclonal gammopathy (480 mg/dL; to convert to milligrams per liter, multiply by 10) and type I cryoglobulinemia (cryocrit concentration, 50%). The serum IgG level was normal (834 mg/dL [reference range, 700-1600 mg/dL]; to convert to grams per liter, multiply by 0.1). An exhaustive diagnostic workup re-
revealed no underlying hematologic disease and no viral infection; a test for autoantibodies had negative results. A diagnosis of cutaneous necrotizing vasculitis associated with type I essential cryoglobulinemia was made. Treatment with oral prednisone (60 mg/d), intravenous pulses of methylprednisolone (500 mg/d for 3 days), and azathioprine sodium (150 mg/d for 3 months) was unsuccessful. Because of uncontrolled vasculitis, off-label therapy with a single cycle of 4 weekly infusions of rituximab at a dose of 375 mg/m² was administered, azathioprine therapy was discontinued, and the prednisone dose was tapered to 50 mg/d, followed by a gradual tapering of 5 mg/mo. This regimen resulted in complete healing of the skin ulcers within 8 weeks. Four months after the completion of rituximab therapy, the patient presented with speech disturbance, behavioral changes, and weight loss. Brain magnetic resonance imaging showed multiple ring-enhancing lesions (Figure). Cerebral toxoplasmosis was suspected and confirmed by means of a polymerase chain reaction test for *Toxoplasma gondii* DNA in the cerebrospinal fluid and the identification of bradyzoites in the brain tissue. The patient was seronegative for human immunodeficiency virus (HIV) and had a normal neutrophil count (4380/µL), normal CD4 and CD8 lymphocyte counts (434/µL and 376/µL, respectively), B-lymphocyte depletion (1 cell/µL), and a low serum IgG level (1.90 g/L [reference range, 7-16 g/L]). The patient tested positive for *Toxoplasma*-specific IgG but negative for IgM, which suggested a reactivation of the disease from a prior infection. Despite treatment with pyrimethamine, sulfadiazine sodium, and folinic acid, the patient’s mental status did not improve.

**Comment.** Toxoplasmosis is an infection caused by the protozoan parasite *T gondii* and can be life-threatening in immunocompromised patients, particularly in transplant recipients and in patients with AIDS. In these individuals, toxoplasmosis almost always occurs as a result of the reactivation of a chronic infection. The seroprevalence of *T gondii* varies greatly among countries, ranging from 15% in the United States to 60% or more in countries with high endemicity such as France.

Treatment with rituximab results in the rapid depletion of CD20+ B cells, which remain at low or undetectable levels for 2 to 6 months before returning to pretreatment levels, generally within 12 months. The mechanism of B-cell depletion seems to be a combination of Fc receptor gamma-mediated antibody-dependent cytotoxicity, complement-mediated cell lysis, and B-cell apoptosis. Adverse events attributed to rituximab include infusion reactions, infections, hypogammaglobulinemia, and delayed-onset neutropenia. Particularly, low serum IgG levels after rituximab treatment are associated with a significantly increased risk of serious infections, with almost a 2-fold increase in risk.

Host resistance in protozoan infections is dependent on both innate and acquired cell-mediated immune responses. In addition, several studies have implicated B cells and antibodies in host survival and protozoan parasite clearance. The relationship between parasitic infections and rituximab treatment remains unclear. Interestingly, 1 case of granulomatous *Acanthamoeba* encephalitis has been reported in a patient who was treated with rituximab and prednisolone for cryoglobulinemia; in addition, a recent study on immunocompromised patients identified rituximab treatment as an important risk factor for persistent and relapsing babesiosis.

Our case emphasizes the need to consider cerebral toxoplasmosis in any patient receiving rituximab with new cognitive or neurologic defects. In our patient, there was a strong temporal relationship between rituximab treatment and the onset of neurologic symptoms, suggesting that rituximab played a decisive role in the development of the opportunistic infection. Indeed, although the patient received corticosteroids, cerebral toxoplasmosis developed only after the rituximab infusions had begun. The patient was not receiving other immunosuppressants concurrently and was HIV negative, the steroid dose was being tapered, and the patient developed a low IgG level following rituximab administration. Low levels of IgG are generally considered to significantly increase the risk of infection. Therefore, screening patients for *Toxoplasma* infection is recommended, and the need for primary prophylaxis against toxoplasmosis in patients who test positive for *Toxoplasma*-specific IgG prior to the use of rituximab therapy remains to be determined and should be evaluated for each patient with a low IgG level.

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Balancing the Risks and Benefits of Rituximab

In this issue, Safa and Darrieux1 report a new and serious type of infection after rituximab therapy: cerebral toxoplasmosis. Although rituximab has helped many patients with lymphoma and autoimmune disease for more than 10 years, it has been linked to several major infectious complications.2 Reactivation of hepatitis B, cytomegalovirus disease, and the rare but fatal progressive multifocal leukoencephalopathy are the most infamous of these infections.

Establishing a causal link between rituximab and infectious complications is difficult because most patients receive multiple immunosuppressants, consecutively or even concurrently. Rituximab can be impressively effective in some patients. More than 40% of patients with non-Hodgkin lymphoma3,4 respond and 30% of patients with rheumatoid arthritis5 improve with this drug, whereas only 1% experience serious infections.6 Balancing these rare but alarming adverse effects with the immediate benefits is not easy. As more patients are prescribed this drug, we must remain vigilant to posttrial data on complications and study ways to help patients and physicians make informed decisions that incorporate the rapidly expanding evidence base concerning potential adverse effects.

Eleni Linos, MD, DrPH

RESEARCH LETTER

Health Care Reform

The Frequency and Characteristics of Dietary Supplement Recalls in the United States

Recently, the US Food and Drug Administration (FDA) has identified an emerging trend in which over-the-counter products, represented as dietary supplements, contain hidden ingredients that could be harmful.

See Editor's Note at end of letter

The FDA defines a dietary supplement as a product taken by mouth that contains a “dietary ingredient” intended to supplement the diet.1 The dietary ingredients in these products may include vitamins, minerals, herbs or other botanical products, amino acids, and substances such as metabolites (eTable; http://www.jamainternalmed.com).

In contrast to pharmaceutical products, federal law does not require dietary supplements to undergo stringent review by the FDA before they are marketed.1 However, the FDA does mandate that manufacturers of these products use current good manufacturing practices to ensure quality throughout the manufacturing, packaging, labeling, and storing of these products.2 Despite these safeguards, dietary supplements adulterated with pharmaceutical compounds have continued to enter the marketplace.2 Their use may expose unwitting consumers to potential harm.

Identification of dietary supplements for recall by the FDA may occur through multiple mechanisms, including spot inspection of manufacturers, tips of potentially adulterated products from retailers, and adverse event reports generated by consumers and physicians to name a few.3 Currently, little is known about the extent to which dietary supplements are recalled owing to their potential to cause serious adverse health consequences or death.