Bilateral ocular myositis as a late complication of dermatomyositis.

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Prasterone and Bone Mineral Density in Women with Systemic Lupus Erythematosus

To the Editor:

We read with interest the report by Mease, et al describing improved bone mineral density (BMD) in glucocorticoid-treated women with systemic lupus erythematosus, after prasterone (DHEA) therapy at 200 mg/day for one year.1 Readers should be aware that DHEA doses of 200 mg/day are clearly supraphysiological. Based on our own clinical and laboratory experience with DHEA therapy, and the scientific literature, doses of DHEA greater than 50 mg/day almost always result in urinary DHEA and DHEA metabolite (androsterone and etiocholanolone) concentrations that are higher than those measured in healthy young adults.

Callies, et al reported that when DHEA 50 mg/day was given to elderly men and women, urinary excretions of DHEA and metabolites were slightly higher than in healthy young adults, while DHEA 100 mg/day resulted in clearly supraphysiological values2. A study of the effects of DHEA on prednisone pharmacokinetics and cortisol suppression in healthy women reported that serum DHEA and DHEA-S were significantly greater than endogenous levels at a dose of 200 mg/day2. The risk of adverse effects increases with increasing DHEA dose3.

In our experience, women receiving DHEA doses of 100 mg/day or higher often have elevated testosterone concentrations in serum and urine, and prominent androgenic side effects.

Some patients may need supraphysiological doses of DHEA. In these cases, monitoring of DHEA and its metabolites would be prudent. Improved BMD in older women after DHEA 50 mg/day has been reported in one study4. Followup studies comparing 50 mg doses of DHEA to the 200 mg dose should be undertaken to evaluate effects on bone density. In any case, based on our experience with thousands of patients receiving DHEA therapy, we recommend laboratory testing for any patient taking 25 mg/day or more. Twenty-four hour urinary steroid hormone profiling may be especially helpful, because it allows determination of DHEA and several downstream metabolites, including androsterone, etiocholanolone, estradiol, estrone, and testosterone.

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Dr. Mease and Dr. Schwartz reply

To the Editor:

Alexander and colleagues have inquired about the rationale for the 200 mg/day dose of prasterone used in our recent study. Our study assessing bone mineral density (BMD) was nested within a larger 381 patient study designed to assess effects of prasterone on overall lupus disease. Women with active systemic lupus erythematosus have low circulating levels of DHEA-S, which are suppressed even further by treatment with exogenous glucocorticoids. Acute effects increases with increasing DHEA dose4. We cited a French study that assessed changes in bone mineral density (BMD) in normal, healthy women aged 60–79 years who received 50 mg/day prasterone or placebo for up to one year. No effects on BMD were observed in men; in women, a positive effect on BMD was observed, mostly in trabecular bone zones. However, few of the multiple comparisons reported were statistically significant, and none of the comparisons for change in BMD at the total hip was significant. Further, they did not report BMD in the lumbar spine and, importantly, these were not patients receiving glucocorticoids.

The metabolism of prasterone is complex, with both downstream androgenic and estrogenic metabolites. Additionally, prasterone may also have direct actions that do not require conversion to downstream androgens or estrogenic metabolites. While measurement of various downstream metabolites is of interest, we believe the most important measurements remain those of serum testosterone, estradiol, and DHEA/DHEA-S.

Finally, it should be noted that prasterone is an investigational agent, currently in testing as a treatment for lupus. There are currently no US Food and Drug Administration-approved indications for its use.

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It was with great interest that I read the article by Kokotis, To the Editor:

Bilateral Ocular Myositis as a Late Complication of Dermatomyositis

To the Editor:

It was with great interest that I read the article by Kokotis, *et al.* describing a patient with bilateral ocular myositis that was, according to the authors, a late complication of dermatomyositis (DM). The article is of interest occurring in a patient several years after dermatomyositis (DM), prompted us to report the following case.

A 71-year-old woman presented in December 1999 with a 3-month history of bilateral ocular myositis that was, according to the authors, a late complication of dermatomyositis (DM). The article is of interest occurring in a patient several years after dermatomyositis (DM), prompted us to report the following case.

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fibrillation was present with heart rate of 80/min. Laboratory evaluation showed antinuclear antibodies (ANA, 1:640, homogeneous pattern), but no other autoantibodies (anti-DNA, antieutryptic nuclear antigen, antineutrophil cytoplasmic antibodies, anticardiolipin, and rheumatoid factor). The other laboratory data were normal, including creatine phosphokinase, C-reactive protein, complement, and thyroid function tests.

Orbital magnetic resonance imaging (MRI) was consistent with inflammatory myopathy of extrinsic ocular muscles. Electromyography (EMG) of arm and leg muscles showed mild involvement confined to deltoid. She refused azathioprine and began methotrexate (MTX), 7.5 mg once a week, with a slow but significant improvement. Orbital MRI was unchanged in June 2000, but by December 2000 did not show any myopathy, even though a mild exophthalmus persisted. MTX was progressively reduced and discontinued. When last seen (March 2004), she was in good health.

As far as we know, this is the second case of bilateral orbital myositis in patients with systemic inflammatory myopathy. Interestingly, our patient, like the patient described by Kokotis, et al., developed orbital myositis several years after systemic muscle involvement, with no other symptoms than proptosis and exophthalmus, and with normal circulating muscle enzymes (Kokotis’s patient reported erythema on the back and eyelid). Several cases of orbital myositis have been reported in association with autoimmune rheumatic diseases²-⁴, however, although our patient had antinuclear antibodies, since there were no symptoms/signs suggesting other rheumatic diseases, since mild signs of myopathy were indeed recorded on EMG, and because of the previous biopsy-based diagnosis of inflammatory polymyositis, we conclude that our patient had bilateral ocular myositis as a late complication of polymyositis.

Another interesting feature that seemed to emerge in both patients was good response to low dose MTX. Our patient was started on MTX, having refused azathioprine and because steroids were contraindicated for severe osteoporosis. Kokotis’s patient did not benefit from azathioprine or intravenous immunoglobulin, but did improve with MTX. Poor response to steroids has been recently reported in a child with idiopathic orbital myositis⁵.

In accord with Kokotis, et al., we conclude that ocular myositis is probably less rare than previously thought and suggest the usefulness of low dose MTX.

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REFERENCES

Dr. Kokotis replies
To the Editor:

We thank Dr. Hengstman for his comments on our article. Our patient pre-
sent with typical red-purple edematous erythema on the upper palpebra (skin lesion), he had myopathic-like changes on electromyography and pathologic findings compatible with inflammatory myositis in muscle biopsy, and had experienced proximal muscle weakness in the past that resolved with prednisone treatment. Therefore, he met the classification criteria for dermatomyositis (DM) according to Tanimoto, et al\(^1\), as well as the proposed revised classification criteria for idiopathic inflammatory myopathies by Targoff, et al\(^2\). Serum creatine kinase or aldolase levels were not measured at the time when proximal muscle weakness was clinically evident. Clearly this is not a case of severe DM, but, as we have stated, represents a mild disease form that was untreated for years. Further, the presence of orbital myositis is fully supported by his clinical condition, i.e., the presence of erythema, eyelid edema, and orbital pain, as well as by magnetic resonance image (MRI) findings. The absence of diplia or ophthalmoplegia, which were also not present in 15% of the 52 patients with orbital myositis reviewed by Berkhoff, et al\(^3\), does not exclude this diagnosis. Indeed, Siatkowski, et al\(^4\) observed normal function of the affected muscles in 34 of 74 patients (45%) with idiopathic orbital myositis.

Unintentionally, we failed to mention that ophthalmopathy associated with Graves' disease was excluded on the basis of normal thyroid function and thyroid autoantibody profile, including thyrotropin receptor antibodies\(^5\). Further, the MRI findings (Figure 1) disclosed not only involvement of the muscle bellies, but also enlargement of the tendons of the orbital muscles. MRI measurements of orbital tissues in thyroid-associated ophthalmopathy have shown that tendons are not affected in patients with Graves' disease\(^6\).

Dr. Marasini and her colleagues report a second case of bilateral ocular myositis that developed 10 years after initial diagnosis of inflammatory myopathy. Their case has striking similarities to our patient, including normal levels of serum muscle enzymes and thyroid function, no diplia or ophthalmoplegia, and a beneficial response to treatment with methotrexate.

To conclude, although we agree that the occurrence of diplia or ophthalmoplegia in a patient diagnosed with polymyositis or DM requires a thorough differential diagnosis to exclude coincidental disease, we feel that our case report as well as the second patient described by Marasini, et al\(^6\) indicate that ocular myositis should not be overlooked in patients with DM.

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**Bacillus Calmette-Guérin Vaccination in a Patient Treated with Infliximab**

To the Editor:

Anti-tumor necrosis factor-α (TNF-α) agents have come into widespread use, and adverse events such as infections are well described complications\(^1\). The infection of greatest concern is tuberculosis (TB)\(^2,3\). Patients receiving TNF-α blockers should not be given a live attenuated vaccine such as bacillus Calmette-Guérin (BCG). The risk of developing BCG related adverse reactions among anti-TNF-α treated patients is not known. We describe a case of BCG vaccination in a patient with rheumatoid arthritis (RA) treated with infliximab.

For 5 years, a 24-year-old woman suffered from symmetrical polyarthritis diagnosed as rheumatoid factor-positive RA. She had no other pertinent medical history. She had had BCG vaccination in her infancy. Since the polyarthritis was not controlled by methotrexate 10 mg weekly and prednisolone 10 mg daily, and she rapidly developed hand joint erosions with significant functional disability, therapy with infliximab (3 mg/kg) was introduced in March 2001, producing a prompt and dramatic improvement. The Disease Activity Score (DAS28) decreased from 4.69 to 2.45 after 3 infliximab infusions. A chest radiograph at that time was normal. No tuberculin skin test was performed. Infliximab was maintained while corticosteroids were progressively tapered to 4 mg prednisolone. Between 2001 and 2004, she received infliximab every 8 weeks, with no adverse events.

A tuberculin skin test was performed by her general practitioner (GP) as a requirement for entrance into nursing school. The skin test was negative. The GP decided to revaccinate the patient with BCG without informing our department. The vaccine (Monovax, Aventis Pasteur, Lyon, France) was administered intradermally in the deltoid region of the left arm August 9, 2004, a few days after her last infliximab infusion. Infliximab treatment was withdrawn and she was seen 3 weeks after vaccination, at which time she had not developed any local reaction and had no fever, asthenia, or cough. On examination, there was no axillary lymphadenitis and the lungs showed no abnormalities. The chest radiograph was still normal and sputum cultures were negative. An anti-tuberculosis treatment (isoniazid 4 mg/kg) was given for 2 months. Nine months after vaccination, she was still asymptomatic with no local reaction, axillary adenitis, fever, or pulmonary symptoms.

BCG is a live attenuated vaccine derived from multiple passages of the wild-type *Mycobacterium bovis*. It is used worldwide for TB prevention and is considered to have an excellent safety profile. Adverse events are rare and include local reactions, lymphadenitis, and disseminated disease\(^4,5\). The frequency of adverse reactions after BCG vaccination ranges from 0.1% to 19%\(^6\). In an Australian study, the adverse event frequency in 918 immunocompetent subjects was 5%, including injection site abscesses, severe local reactions, and lymphadenitis\(^6\). Serious disseminated BCG reaction occurs in 2 cases per 1 million vaccinated children, and has been reported mainly in immunocompromised hosts, particularly in persons positive for human immunodeficiency virus (HIV)\(^6\). The factors influencing the occurrence of these BCG adverse reactions are the dose and strain...
of BCG vaccine, the injection technique, and the age and immune status of the vaccinated person1,2,3. Disseminated BCG disease causes fever, weight loss, lymphadenopathy, severe illness, and pulmonary symptoms. Talbot, et al reported one case of disseminated BCG disease in an HIV-negative infant and reviewed another 27 cases, mostly associated with immunodeficiency, including 9 patients with acquired immunodeficiency syndrome4.

In BCG infected mice, TNF-α is required for granuloma formation and mycobacterial elimination, and TNF-α messenger RNA has been detected in granulomas5. Thus, BCG vaccine must be considered a potent active mycobacterium in anti-TNF-α treated patients. However, several substrains of BCG exist that may have different virulence and reactivity. Our patient did not develop any reaction to BCG vaccination. This might indicate that the BCG substrain used for inoculation had low virulence or a good safety profile. An alternative explanation might be the efficacy of the isoniazid treatment, since the BCG substrains used in France are highly sensitive to this drug. The duration of isoniazid treatment in our patient was empirical. Although BCG disseminated disease usually occurs a few months after vaccination, rarely later4, caution is required before reintroducing anti-TNF-α therapy, and it is difficult to decide when the anti-TNF-α agent should be reintroduced in this situation.

Light of these observations, BCG vaccination should be avoided in patients taking TNF-α blockers. In case of accidental BCG administration, anti-tuberculosis prophylaxis is strongly recommended, the choice of anti-tuberculosis drug depending on the BCG substrain. This case also highlights the importance of education, in particular regarding vaccinations, in patients receiving anti-TNF-α therapy.

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Simultaneous Presentation of Cryptococcal Meningitis and Lupus Nephritis

To the Editor:

Infection is a significant cause of morbidity and mortality in systemic lupus erythematosus (SLE)1. Patients with lupus are known to be at heightened risk for common pathogens as well as opportunistic pathogens2. Susceptibility to infection may be attributed to underlying immune dysregulation and to immunosuppressive therapy. Clinicians caring for these patients need to be familiar with the range of potential pathogens and maintain a high index of suspicion for infection whenever new symptoms or fevers occur. Indeed, severe life-threatening infection can not only mimic but can present simultaneously with new-onset lupus, based on our recent experience.

A 30-year-old woman originally from Guatemala presented to the Johns Hopkins Hospital with acute renal failure. She was well until 2 months prior to admission, when she developed gradual onset of fatigue with intermittent diffuse abdominal discomfort and nausea. One week prior to admission, she developed diffuse myalgias and arthralgias involving the knees, hands, and wrists and pleuritic chest pain. Several days prior to admission she complained of a bitemporal headache without photophobia. Upon hospitalization, she was febrile. She had no rash, oropharyngeal ulcers, or synovitis. Meningismus was absent; mental status and peripheral neurologic examination were unremarkable. Admission examinations included serum creatinine of 4.4 mg/dl and white blood cell (WBC) count of 2300 cells/mm³. Erythrocyte sedimentation rate was elevated at 102 mm/h. Profound hypocomplementemia was present, with C3 24 mg/dl and C4 3 mg/dl. Antinuclear antibody titer was 1:640. Anti-doble-stranded DNA titer was markedly elevated at 1:640. Chest computer tomography scan revealed pleural and pericardial effusions. Renal histopathology showed WHO class IV glomerulonephritis with numerous crescents.

Based on these findings she was diagnosed with SLE. The headache was initially attributed to lupus disease activity. Intravenous methylprednisolone was initiated at 1 gm/day for 3 consecutive days, followed by oral prednisone 60 mg/day. Given the severity of renal disease, intravenous cyclophosphamide was administered at 750 mg/m². The day after cyclophosphamide infusion, she developed fever. She continued to have a mild intermittent headache and no abnormalities detected by neurologic or fundoscopic examination. Lumbar puncture revealed normal cerebrospinal fluid (CSF) protein and glucose concentrations and only 1–2 WBC/mm³, but both CSF and blood cultures grew Cryptococcus neoformans.

She was treated with a 14 day course of liposomal amphotericin, followed by a 42 day course of fluconazole, with prompt resolution of the fever and headache. Corticosteroids were gradually tapered. Subsequent blood and CSF cultures one month after diagnosis were negative for fungal growth. She did require hemodialysis at the time of discharge, but was not given additional cyclophosphamide during the hospitalization.

A large variety of organisms have been reported in association with SLE including bacteria, mycobacteria, viruses, fungi, and protozoa3. Moreover, infections are reported to account for 14% of hospital admissions in affected persons3. Whether susceptibility to infection is due to immunosuppressive treatment only or to the underlying disease is uncertain.

Glucocorticoid and cytotoxic drugs may suppress the immune system and heighten susceptibility to infection. Infection rates are reported to be 2–4 times higher in patients treated with compared to those treated without steroids4. Interestingly, there may be inherent immunologic abnormalities associated with lupus that also predispose to infection. Studies conducted prior to the widespread use of immunosuppressive therapies indicated an elevated
risk of infection in lupus⁴. Further, deficiencies of complement components, which are known to predispose to development of lupus⁵, may also lead to impaired clearance of immune complexes and microbial pathogens⁶-⁷. Specifically, patients with lupus who possess deficient mannos-binding lectin are at higher risk for serious infection⁸.

Cryptococcal meningitis is an uncommon complication of SLE. Most reports of cryptococcal disease in lupus describe patients who have been maintained on high levels and sustained durations of immunosuppressive therapy. Zimmermann, et al reported 2 new cases and reviewed the literature regarding 24 previous cases⁹. Mean duration of lupus at development of cryptococcal meningitis was 3.3 years. Twenty-four of these patients were treated with corticosteroids and 10 with azathioprine. The outcome without antifungal therapy was uniformly poor, and all 5 untreated patients died. In contrast, there were 8 deaths in the 20 patients treated with amphotericin. Further, there has been one previous report of a patient who developed cryptococcal meningitis concurrent with the diagnosis of SLE and prior to initiation of immunosuppressive therapy¹⁰.

Our case represents the second report of a patient diagnosed with cryptococcal meningitis simultaneously with onset of SLE. We believe the unusual presentation suggests that underlying immune defects associated with lupus contributed to their infection, since both cases became clinically apparent before receipt of prolonged immunosuppression.

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