Acne vulgaris is a common condition in adolescents, affecting as many as 81% to 95% of boys and 79% to 82% of girls. While treatment for mild acne typically consists of the use of topical creams, treatment for moderate to severe acne normally involves the use of oral antibiotic therapy. In recent years, however, minocycline has been under increasing scrutiny as a medication because of its long half-life, frequent bacterial resistance to the medication, enhanced tissue absorption, and improved patient compliance. In the United States, minocycline is one of several medications prescribed for the treatment of moderate to severe acne because of a lack of substantiation of the claims of its superiority to other oral antibiotics. In addition, minocycline has been linked to potentially severe and even life-threatening adverse reactions such as drug-induced lupus (DIL), hepatic damage, dyspnea, severe hypoxia, and pulmonary infiltrates.

**Drug-Induced Lupus**

As far back as 1945, DIL has been associated with medication use. In 1988, Hess presented a pathological classification scheme for DIL that consisted of the following criteria: no history of systemic lupus erythematosus (SLE), the presence of positive antinuclear antibodies (ANAs), the presence of at least 1 clinical feature of SLE (TABLE 1), and an improvement in symptoms with the discontinuation of the medication.

Symptoms of DIL can vary based on the offending medication. Clinical symptoms are similar to those of SLE in that arthralgia, arthritis, myalgia, fever, and malaise are often present. Drug-induced lupus differs from SLE in that there is less of a discrepancy in the male-female ratio, skin involvement is dependent on the specific medication in DIL but is generally less common than in SLE, and renal involvement is comparatively less frequent in DIL than in SLE. Testing positive for ANAs is a common finding in SLE and in DIL. However, testing positive for antibodies to double-stranded DNA is common in SLE but is rare in DIL. In SLE, the ANAs and the antibodies to double-stranded DNA are theorized to bond with their common antigen, resulting in immune complexes that are deposited in the skin (in the case of discoid lupus erythematosus) or in vascular tissues throughout the body.
(in SLE). Although (to my knowledge) the exact pathogenic mechanism of DIL has not been identified and may vary depending on the medication involved, the production of reactive metabolites that trigger a similar immune response has been hypothesized. Despite the mechanism, once the offending medication is discontinued, the effects of DIL typically begin to resolve immediately and completely resolve within a few weeks to months.10,14,34

Since the initial description of DIL, as many as 70 medications have been linked to DIL, accounting for up to 10% of the cases of lupus annually in the United States.41 TABLE 2 lists the common medications linked to DIL. Several other medications, including anticonvulsants, antithyroids, β-blockers, thiazide diuretics, sulfasalazine, and d-penicillamine, could be capable of producing DIL, but further substantiation of the link is necessary.44 Other commonly prescribed medications such as angiotensin-converting enzyme inhibitors and statins are suspected of having a link with DIL, but significant evidence to support these suspicions is lacking to date.41

Minocycline, a semisynthetic derivative of tetracycline commonly used as an oral antibiotic to treat infections and moderate to severe acne and as an oral antibiotic to treat infections and moderate to severe acne and as a disease-modifying antirheumatic drug, was initially linked to DIL via reports in the medical literature in the early 1990s.42,37 Since that time, more than 70 cases of minocycline-induced lupus have been reported.41 The suspected link between minocycline use and DIL was strengthened by a body of evidence that demonstrated that the signs and symptoms subsided with the discontinuation of minocycline treatment and recurred with the reintroduction of minocycline treatment.30,14,18,32,34 In 1999, Elkayam et al59 classified minocycline-induced syndromes as serum sickness, DIL, autoimmune hepatitis, and vasculitis. In 2000, Lawrenson et al33 performed a systematic literature review that confirmed the further division of minocycline reactions into hypersensitivity reactions and late-onset or autoimmune hepatitis. Hypersensitivity reactions such as serum sickness were found to occur within 1 month of the initiation of minocycline therapy, while autoimmune hepatitis and vasculitis typically occurred after 1 year or more of therapy.19,22,26,33 Other members of the tetracycline family have been associated with hypersensitivity, serum sickness, and single organ dysfunction reactions that can also cause arthralgia and hepatitis.43 However, to my knowledge, minocycline is the only member of the tetracycline family to be linked conclusively to DIL.43,46

Because minocycline therapy has the potential for harmful adverse reactions, many authors have confirmed the need for physicians to perform pharmacovigilance, or monitoring of the safety of minocycline drug therapy regimens, to detect serious adverse effects.24,30,33,46 As physical therapists strive toward the goals of Vision 20203 and toward recognition as providers of choice for musculoskeletal dysfunctions, their ability to perform pharmacovigilance will become even more vital.

The objective of this resident’s case problem is to illustrate the importance of physical therapists’ including a pharmacovigilance component in their patient examination and evaluation processes. Specifically, this case will address the relevance of screening for minocycline-induced lupus in adolescents and in patients with rheumatoid arthritis. However, these principles can easily be expanded to the signs and symptoms related to reactions to other medications.

### History of Illness

The patient was a well-conditioned active 15-year-old adolescent boy who participated in a competitive basketball league and other interscholastic sports. Three weeks before the examination by the physical therapist, the patient had been using the topical ointment tazarotene (Tazarac) for acne, with minimal results. At that time, he visited his family physician, who prescribed minocycline at a daily dosage of 100 mg. The patient reported that 1 week before the examination by the physical therapist (2 weeks after starting minocycline) he awoke with a fever of 103°F, swollen eyes, and swollen lips. The patient was seen by his family physician, who reportedly made
a diagnosis of sinusitis and prescribed telithromycin (Ketek), a semisynthetic antibacterial medication in the ketolide class of antibiotics. Minocycline was discontinued with the initiation of telithromycin. Four days before the examination by the physical therapist, the patient reportedly experienced a truncal rash and hives on his extremities, at which time his family physician discontinued telithromycin and prescribed a methylprednisolone dose pack. The patient reported swollen elbow joints the following day, but otherwise his symptoms had improved. One day before the examination by the physical therapist, the patient began to experience bilateral calf pain, right hip pain, and right shoulder pain and weakness.

The patient had been previously treated by the examiner for Osgood-Schlatter disease, and he presented for examination without physician referral after the onset of his musculoskeletal symptoms. The patient’s chief complaints were myalgia (moderate calf pain bilaterally), arthralgia (severe right hip and right shoulder pain) and right shoulder weakness, general fatigue, and malaise. The patient reported normal bowel and bladder function. The patient’s mother reported normal bowel and bladder function. The patient’s mother reported normal bowel and bladder function.

**Social and Medical History**

The patient lived with his mother, and his father was deceased. The patient’s family history was significant for hypertension, diabetes mellitus, and epilepsy. The patient’s medical and surgical history was unremarkable except for excision of a cyst as an infant and for Osgood-Schlatter disease.

**DIAGNOSIS**

**Physical Examination and Evaluation**

The patient’s heart rate was 84 beats/min, and his oral temperature was 99.4°F. The patient’s weight was 63.2 kg (decreased from 68.2 kg at his physician visit 1 week prior). The patient’s pain level was assessed on a visual analog scale (range, 1-10), and calf pain was determined to be 4 at its best and 6 at its worst bilaterally, while right shoulder and right hip pain was reported at a minimum of 6 and a maximum of 9. No edema or erythema was observed in the patient’s ankles, calves, hands, wrists, or elbows at the time of the examination. Circulation was adequate throughout the patient’s extremities, and good capillary refill was noted. Homan sign was negative, and there were no skin or temperature changes noted. The patient’s score on the clinical decision rule for deep vein thrombosis described by Riddle and Wells40 was less than 0, indicating less than a 3% chance of deep vein thrombosis.

The patient had only 52° of right shoulder flexion passive range of motion and 31° of right shoulder flexion active range of motion. All other active and passive right shoulder motions were severely limited secondary to pain. Likewise, right hip active and passive ranges of motion were severely limited (at 47° and 29°, respectively) because of pain. The patient’s functional strength in the involved joints was severely limited and could not be formally assessed because of pain. Despite unilateral shoulder pain, the left shoulder strength was also limited to fair for flexion and for abduction. Other than the left shoulder, the strength in uninvolved joints was generally fair to good minus throughout the patient’s left upper and lower extremities.

The patient’s gait and balance were also impaired. The patient had increased hip and calf pain with weight bearing that resulted in an antalgic gait and an inability to walk without support. Stance time was severely limited on the right, and the patient demonstrated signs of distress (teeth clenched, breath held, flushing, increased heart rate, and tremor) when attempting to ambulate.

The patient’s reflexes were 2+ (normal) for biceps, brachioradialis, triceps, and Achilles tendons and 3+ (slightly hyperreflexive) bilaterally for the quadriceps tendons. A Trendelenburg test was not tolerated, as the patient could not maintain a single-limb stance on either lower extremity because of pain. Likewise, the patient could not tolerate a prone position for an Ely test to assess rectus femoris flexibility or a repositioning for a Thomas test to assess tightness of the hip flexors. Palpation of the right shoulder and right hip revealed diffuse pain over both joints, but no specific point tenderness was noted in either area.

The evaluation was based on data that were gathered from the history, review of systems, and test results and

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**TABLE 2**

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>INDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>Severe hypertension</td>
</tr>
<tr>
<td>Procainamide hydrochloride</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Various forms of mental illness</td>
</tr>
<tr>
<td>Quinolones</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Infection, acne, rheumatoid arthritis</td>
</tr>
</tbody>
</table>

*From Sarzi-Puttini et al.*
Diagnosis
The patient was seen by a pediatric rheumatologist at a tertiary children’s hospital 7 days after the initial physical therapy examination. The patient underwent extensive blood work, which was negative for Lyme disease, acute mononucleosis or Epstein-Barr virus, and rheumatoid factor. Radiographs did not reveal any signs of osteoarthri-

DISCUSSION

Outcomes
One month after the initial examination, the patient demonstrated functional and pain-free active and passive right hip and right shoulder range of motion. Calf pain was also completely resolved. His strength improved to fair plus for both shoulders and to good throughout the remainder of the upper and lower extremities. His gait was generally normal, but decreased endurance was noted, especially on hills and stairs. The results of special tests of the shoulder joint (crank test, apprehension test, Hawkin test, Yergason test, and empty can test) were negative, with no signs of compromised joint integrity, mobility, or impingement noted. Similar findings were noted for the right hip (negative Thomas test, Trendelenburg test, Ely test, and Ober test results). Coordination had improved but was mildly impaired, as the patient still had difficulty with high-level coordination skills. The residual strength, endurance, and coordination deficits continued to limit the patient’s ability to play basketball.

Two months after the initial examination, his bilateral shoulder strength improved to good, and the strength in all other joints was approaching normal

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Patient’s Level</th>
<th>Normal Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine level (mg/dL)</td>
<td>0.7</td>
<td>0.8-1.5</td>
</tr>
<tr>
<td>Alkaline phosphatase level (U/L)</td>
<td>170</td>
<td>38-126</td>
</tr>
<tr>
<td>Aspartate aminotransferase level (U/L)</td>
<td>47</td>
<td>15-46</td>
</tr>
<tr>
<td>Alanine aminotransferase level (U/L)</td>
<td>72</td>
<td>11-66</td>
</tr>
<tr>
<td>Creatine phosphokinase level (U/L)</td>
<td>24</td>
<td>55-170</td>
</tr>
<tr>
<td>Lymphocyte count (%)</td>
<td>28</td>
<td>50-56</td>
</tr>
<tr>
<td>Atypical lymphocytes (%)</td>
<td>32</td>
<td>0</td>
</tr>
<tr>
<td>Lyme disease antibody screen</td>
<td>&lt;0.75</td>
<td>&lt;0.75</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>12</td>
<td>0-15</td>
</tr>
<tr>
<td>Presence of antinuclear antibodies</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

SI conversion factor: to convert creatinine to micromoles per liter, multiply by 88.4.
levels. The patient’s gait had returned to normal, and he could walk at a moderate speed (4.0–4.8 km/h) for at least 30 minutes. However, his endurance was still limited for athletic activities such as basketball. At this point, the patient could shoot a basketball successfully, although his skills had not yet improved to premedication levels. No weight gain was noted.

Three months after the initial examination, the patient’s strength had returned to normal at all joints. Coordination also had improved, and the patient could now participate in basketball at premedication levels except for endurance limitations, as he still required frequent rest periods because of fatigue.

Four months after the initial examination, the patient had returned to his premedication activity levels except for his weight, which was still 4.5 kg below his prior weight. Full weight recovery was achieved by 10 months after the initial examination.

Clinical Implications

The patient described in this case report demonstrated clinical characteristics that were comparable to clinical characteristics of patients with DIL that have been reported in the literature. Gordon and Porter reported that during a 5-year period 20 patients receiving minocycline therapy in Scotland experienced polyarthritis (inflammation of multiple joints), polyarthralgia (pain in joints), and at least 1 extra-articular feature such as myalgia, fevers, lethargy, and abdominal pain. Shepherd described a patient who experienced fever, malaise, fatigue, and weight loss following minocycline therapy. Akin et al detailed the histories of 5 adolescent girls whose symptoms of minocycline-related reactions included fatigue, arthralgia, myalgia, fever, and polyarthritis, along with elevated alanine aminotransferase and aspartate aminotransferase levels. Lawson et al also reported symptoms of polyarthritis, malaise, myalgia, and morning stiffness in patients undergoing minocycline therapy. Landau et al described a patient who experienced urticaria, fever, and arthritis within 15 days of beginning minocycline therapy. Much like the patient outlined herein, Tournigand et al presented a patient who while taking minocycline experienced calf pain that increased during 4 days until walking became progressively impossible. Gough et al reviewed the clinical presentation of 11 patients who were diagnosed as having minocycline-induced lupus and found that all presented with polyarthralgia and polyarthritis. Likewise, Schlienger et al retrospectively reviewed 57 subjects with DIL and found that polyarthralgia and polyarthritis were present in all 57 subjects. In addition, Elayam et al described 7 patients taking minocycline who presented with polyarthritis, polyarthritis, morning stiffness, and fever. Finally, Byrne et al highlighted 5 patients taking minocycline who presented with arthralgia and arthritis, all of whom demonstrated positive ANAs.

Teitelbaum et al questioned whether a lack of awareness among pediatricians because of a lack of evidence about DIL in the pediatric literature resulted in missed diagnoses and in underreporting of minocycline-induced reactions. Similarly, because minocycline is used in the treatment of rheumatoid arthritis, multiple authors hypothesized that minocycline-induced symptoms could be easily misinterpreted as an exacerbation of rheumatoid arthritis. Marzo-Ortega et al presented a case of minocycline-induced lupus in a patient with rheumatoid arthritis and questioned whether this adverse reaction is underreported because of misinterpretation as an exacerbation of rheumatoid arthritis. Eichenfeld concluded that a need exists for increased awareness of the potential adverse reactions to minocycline therapy among physicians who treat rheumatoid arthritis. Such a need could be expanded to physical therapists as well.

In addition to insufficient information in the nondermatology and rheumatology literature, the diagnosis of minocycline-related reactions is complicated by the fact that, unlike the patient in this report, reactions often occur after 1 year of minocycline therapy. In these instances, patients rarely make a connection between the medication used and the musculoskeletal symptoms, and they often forget to list minocycline as a medication used altogether. Complicating this scenario is the fact that acne is typically well controlled with minocycline use, so there are usually no obvious physical signs of acne that would alert a provider to minocycline therapy. These factors demonstrate the need for medical providers, including physical therapists, to perform a thorough and comprehensive history of medication use. In addition, providers should not rely solely on the written history provided by patients but rather should perform a verbal medication inquiry, asking specifically about minocycline therapy when examining adolescents, young adults, and patients with rheumatoid arthritis. This will aid in the accurate identification of minocycline-related signs and symptoms.

The importance of understanding pharmacology and pharmacovigilance has been illustrated in physical therapy textbooks and in peer-reviewed physical therapy journals. Physical therapists can improve their proficiency with pharmacovigilance by becoming familiar with medications that are commonly used in their patient caseload and by having a general awareness of potential adverse reactions to such medications. The importance of the physical therapist’s ability to screen for risk factors and for medication reactions was highlighted by Boissonnault and Meek in their investigation of the prevalence of risk factors for anti-inflammatory drug or aspirin-related gastrointestinal complications. Boissonnault and Meek
found that physical therapists could potentially minimize the risk of serious gastrointestinal complications by including a pharmacovigilance component in their patient examination process. While the need to be aware of adverse reactions to commonly used medications such as anti-inflammatory drugs has been identified, the case described herein illustrates the importance of the physical therapist’s ability to identify reactions to medications that are used less commonly.

Familiarization with medication reactions can be complicated by the fact that information regarding adverse medication reactions may be reported primarily in specialty journals (in this case, the dermatology and rheumatology literature) rather than in journals that are commonly read by physical therapists. Access to relevant articles in nonphysical therapy journals can often involve a significant financial investment to obtain full-text versions. The shear volume of the medical literature complicates physical therapists’ ability to keep abreast of updated pharmacologic findings on a routine basis. With the proliferation of electronic databases, open access to a automated medication monitoring system would provide all health care providers, including physical therapists, with an uncomplicated means of accessing current information on medications and adverse reactions.

In conclusion, the use of a pharmacovigilance component in the patient examination process can augment the physical therapist’s ability to identify when neuromusculoskeletal symptoms are derived from pathological rather than mechanical conditions. Accurate identification of drug-related symptoms allows for prompt physician referral and timely treatment for the patient. Failure to identify drug-related symptoms can subject a patient to prolonged illness with further deterioration, unnecessary psychological stresses, and invasive investigations or treatments. This resident’s case problem highlighted a patient who presented with musculoskeletal symptoms that resulted from a medication reaction rather than from a mechanical origin. It illustrates the potential role of the physical therapist in performing pharmacovigilance.

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