Osteomyelitis in Patients with Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To investigate the clinical profile of and the risk factors for osteomyelitis in patients with systemic lupus erythematosus (SLE).

Methods. We reviewed 11 consecutive cases of patients with SLE who had also had osteomyelitis between 1981 and 2001 at a medical center in Taiwan, with special attention to predisposing factors, clinical features, laboratory values, and outcomes.

Results. The mean age at diagnosis of osteomyelitis was 34.5 ± 22.0 years and the ratio of females to males was 9:2. The typical initial manifestations were nonspecific focal pain (82%) and fever (64%). The most commonly affected sites were the long bones (6 cases, 54%), followed by the vertebrae (4 cases, 36%). *Salmonella* (5 cases, 45%) and *Staphylococcus aureus* (4 cases, 36%) were the major causative organisms. Interestingly, once long bones had become involved, 5 of 6 (83%) isolates proved to be *Salmonella*, and for vertebral osteomyelitis, 3 of 4 (75%) isolates proved to be *S. aureus*. Predisposing factors include an active status of SLE (SLEDAI score ≥ 4, 100%), coexistent underlying systemic disease (91%), chronic renal disease (82%), and intensified immunosuppressive agent usage (82%). Laboratory values either reflected an acute phase reaction that would be expected in an infection, such as a raised C-reactive protein (100%) and neutrophilia (55%), or reflected features consistent with active lupus disease. Four patients had longterm motor deficits and another patient died. Poor prognostic factors include delayed diagnosis, vertebral involvement, artificial implants in bones, and chronic carrier status.

Conclusion. In patients with SLE who present with local osteoarticular pain, particularly those whose disease is active and who also have chronic renal disease and were taking intensified immunosuppressive agents, osteomyelitis must be considered seriously. *Salmonella* should be considered as a potential contributing pathogen for long bone osteomyelitis and *S. aureus* should be considered for cases of vertebral osteomyelitis when conducting empirical antimicrobial therapy. Early recognition and treatment is essential to avoid longterm sequelae or death. (J Rheumatol 2004;31:1340–3)

Key Indexing Terms:
OSTEOMYELITIS
SYSTEMIC LUPUS ERYTHEMATOSUS
SALMONELLA
STAPHYLOCOCCUS AUREUS

Infection is a serious problem for immunocompromised patients. A recent study revealed that infectious complications occurring in the course of systemic lupus erythematosus (SLE) involve mainly the respiratory and urinary tracts[1]. Osteomyelitis among patients with SLE has been rarely reported[2-10], and mostly as case reports. It is worth noting that the protean manifestation of SLE may mislead clinicians into delaying the diagnosis of osteomyelitis, and such delay might result in longterm disability. Also notable is that *Salmonella*, an uncommon pathogen for osteomyelitis in normal hosts, has repeatedly been reported to be associated with osteomyelitis in patients with SLE[2-4,6-9]. To clarify the clinical characteristics of and the potential risk factors for osteomyelitis among patients with SLE, we analyzed 11 consecutive cases diagnosed at a medical center.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of SLE patients who had also had osteomyelitis between 1981 and 2001 at Chang Gung Memorial Hospital in Taiwan. Chang Gung Memorial Hospital is a tertiary teaching medical center, treating about 12% of the overall admissions in northern Taiwan. All cases fulfilled the 1982 American Rheumatism Association revised classification criteria for SLE[11]. A definitive diagnosis of osteomyelitis was made by signs and symptoms suggestive of bone infection, technetium 99m diphosphonate bone scintigraphy, and concomitant culture of causative organisms from sterile sites including blood, urine, synovial fluid, bone biopsy specimen and sputum. All cases were followed for at least 12 months after the diagnosis of osteomyelitis. From 10,732 inpatient records of 3128 SLE patients, 11 consecutive cases were identified and the records were reviewed in detail for clinical features, laboratory values, causative pathogens, sites of bone involvement, predisposing

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Submitted June 6, 2003; revision accepted January 14, 2004.

factors, and outcomes. We also reviewed cases previously reported in the literature.

RESULTS

Pertinent characteristics of the 11 patients are summarized in Table 1. The mean age at diagnosis of osteomyelitis for 11 patients was 34.5 ± 22.0 years (range 8–73) and the female to male ratio was 9:2. The mean age at onset of SLE for these patients was 30.5 ± 21.7 years. The interval between the diagnosis of SLE and that of osteomyelitis ranged from 3 to 204 months (mean 48.8 ± 64.7 mo).

Pathogens and locations. *Salmonella* (5 cases, 45%) and *Staphylococcus aureus* (4 cases, 36%) were the 2 major causative pathogens, the remaining being *Mycobacterium tuberculosis* and *Serratia* (one case each, Table 1). The most commonly affected sites were the long bones (54%, tibia in 4 cases and femur in 2 cases). The next common location was one or more vertebra(e) (36%, thoracic spine in 2 cases and lumbar spine in 2 cases).

Predisposing factors. The SLE Disease Activity Index (SLEDAI) was employed as a scale for defining an SLE flare. Table 1 shows that all osteomyelitis episodes occurred during periods of active SLE activity (100% SLEDAI score ≥ 4). Ten of the 11 cases (91%) coexisted with underlying systemic disease, 8 cases (73%) revealing 2 or more such coexisting diseases. The most frequent underlying disease was chronic renal disease (9 cases, 82%), including renal insufficiency/failure (5 cases), proteinuria (5 cases), and hematuria (5 cases). Other associated illnesses were hypertension (7 cases), central nervous system disease (4 cases), hypertensive cardiovascular disease (2 cases), cholelithiasis (2 cases), inferior vena cava syndrome (1 case), rheumatoid arthritis (1 case), and miliary tuberculosis (1 case) (Table 1). Immunosuppressive drug treatment proved to be another important predisposing factor for osteomyelitis. In the preceding 6 months before the onset of osteomyelitis, all patients had been taking corticosteroids, and the dosage in 6 of them (55%) was increasing. The mean daily dose of prednisolone within the one-month period preceding infection was 29 mg. At the onset of osteomyelitis, 9 of the 11 cases (82%) were taking other immunosuppressive agents, including hydroxychloroquine (n = 6), azathioprine (n = 3), pulse methylprednisolone (n = 2), cyclophosphamide (n = 2), and mycophenolate mofetil (n = 1).

Table 1. Characteristics of SLE patients with osteomyelitis.

Patient	Age	Sex	SLE-OM Dx (mo)	Pathogen	SLEDAI	Bone Affected	Underlying Systemic Disease	Osteoarticular Underline	Cellulitis/ Sep.Arthritis	Diagnosis Methods	S/S-OM Dx	Outcome
1	8	M	9	*S. aureus*	4	T6–T12	HT, CRD	None	+/–	BS, BC, MRI	4 days	Cured
2	15	F	5	*S. enteritidis* D_1	11	Distal femur	CNS	AVNFH	–/–	BS, BC, BYC, UC	0 days	Cured
3	15	F	13	*S. enteritidis B*	4	Distal femur	HT, CRD	None	–/+	BS, BC, BYC, SFC	7 days	Cured
4	15	F	41	*S. enteritidis B*	14	Proximal tibia	HT, IVC, CRD	None	+/–	BS, BC, UC	0 days	Cured
5	51	F	41	*Serratia marcescens*	12	Distal tibia	HT, CRD, CNS, HCVD, cholelithiasis	Gout	+/+	BS, BC, BYC SFC	7 days	Died
6	25	M	21	*S aureus*	10	Toe	HT, CRD	Gout	+/+	BS, BC, BYC, SFC	3 mo	Cured
7	73	F	3	*S. aureus*	7	T11	CRD, cholelithiasis	Degeneration osteoporosis	–/–	BS, BC, MRI	3 mo	Deficit
8	27	F	36	*S. enteritidis B*	12	Tibia	CRD	AVNFH, implant	+/–	BS, BC, BYC	3 mo	Deficit
9	36	F	204	*S. enteritidis B*	4	Distal tibia	None	Trauma, implant	+/+	BS, BC, SFC, BYC	3 days	Cured
10	54	F	144	*S. aureus*	16	L1	HT, CRD, CNS, HCVD, RA	Degeneration osteoporosis	–/–	BS, BC, MRI	2 mo	Deficit
11	61	F	20	*M. tuberculosis*	8	L5	HT, CRD, CNS, miliary TB	Degeneration osteoporosis	–/–	BS, BYC, MRI SpC	2 mo	Deficit
Total	34.5 ± 22.0		48.8 ± 64.7	*Salmonella* 5 *S. aureus* 4		Long bone 6 Vertebrae 4 Other 7	HT 7 CRD 9 CNS 4			BS 11 MRI 4 BC 10 BYC 7 UC 2 SFC 4		

SLE: systemic lupus erythematosus; SLE-OM Dx: interval between SLE and diagnosis of osteomyelitis; SLEDAI: SLE Disease Activity Index; HT: hypertension; CRD: renal disease; CNS: central nervous system lupus; IVC: inferior vena cava syndrome; HCVD: hypertensive cardiovascular disease; RA: rheumatoid arthritis; TB: tuberculosis; AVNFH: avascular necrosis of femoral head; Sep. arthritis: septic arthritis; BS: bone scan; MRI: magnetic resonance imaging; BC: blood culture; UC: urine culture; SFC: synovial fluid culture; BYC: culture from bone biopsy; SpC: sputum culture; S/S-OM Dx: interval between local pain and diagnosis of osteomyelitis.

Clinical features and concurrent infections. Nine cases (82%) revealed focal swelling with some pain, and 7 cases (64%) exhibited fever. Ten of the 11 cases (91%) had concurrent infections. Bacteremia was identified in 10 cases. Cellulitis (6 cases) and septic arthritis (4 cases) were also common associated infections. Two cases experienced urinary tract infections (Patients 2 and 4) and 2 cases developed lobar pneumonia (Patients 7 and 11). Ongoing miliary tuberculosis, a herpes zoster skin infection, and a herpes simplex skin infection were observed in one case each (Patients 11, 4, and 2, respectively).

Laboratory values. Laboratory values either reflected an acute phase reaction as would be expected in an infection, such as a raised C-reactive protein (CRP; 100%) and neutrophilia (55%), or features consistent with active lupus disease such as anemia (91%), lymphopenia (82%), proteinuria (50%), hematuria (50%), raised anti-dsDNA titer (43%), decreased complement 3 (11%), decreased complement 4 (10%), and thrombocytopenia (10%).

Treatments and outcomes. The time between the onset of suspicious symptoms of osteomyelitis and diagnosis ranged from 0 days to 3 months. Antibiotics were given empirically initially in all cases when osteomyelitis was suspected, then switched to the final appropriate antibiotic regimen based upon the results of susceptibility tests *in vitro* or upon the patient's clinical response. Six cases recovered completely with no residual bony damage. Recorded complications included pathological fracture with non-union for 3 cases (Patients 7, 10, and 11) and persistent sinus discharge for one case (Patient 8), which forced these patients to experience longterm motor deficits. Further, one case (Patient 5) died from overwhelming infection. Analysis revealed that probable contributing factors responsible for these complications included delayed diagnosis and treatment (Patients 5, 7, 10, 11), vertebral involvement (Patients 7, 10, 11), artificial implants in bones (Patient 8), and chronic carrier status with recurrent infection by the same species (Patient 5).

DISCUSSION

Infection remains a major source of morbidity and mortality for SLE patients worldwide[12]. With the greater use of immunosuppressive drugs, opportunistic pathogens and new sites of infection such as osteoarthritis have progressively become greater problems[1]. Although the most common pathogen of osteomyelitis for normal hosts has been reported to be *S. aureus*[13], several investigators have shown that for patients with SLE, osteomyelitis is often attributable to *Salmonella*[2-4,6-9] (Table 2). Indeed, *Salmonella* appeared to be the most frequent pathogen for osteomyelitis in our SLE patients, accounting for 46% of all isolates. The second common pathogen was *S. aureus* (36%). *S. aureus* has not been reported previously to cause osteomyelitis in SLE patients[2-10]. Traditionally, it has been believed that *S. aureus* osteomyelitis typically resulted from an infection secondary to local trauma or injury[14], but in our study there were only 2 osteomyelitis patients suffering concurrent cellulitis. Osteomyelitis for the remaining 2 patients was caused by bacterial seeding of *S. aureus* bacteremia. Our study revealed that the most commonly affected sites were the long bones (54%), followed by the vertebrae (36%). An interesting finding was that 5 cases of osteomyelitis caused by *Salmonella* were universally present in long bones, and 75% of osteomyelitis caused by *S. aureus* (3 in 4 cases) was located in vertebrae. From a different perspective, once osteomyelitis of long bones has arisen in SLE patients, in about 83% the causative pathogen will likely be *Salmonella*, while if vertebral osteomyelitis occurs, in around 75% of cases, the causative pathogen will likely be *S. aureus*. The mechanism for the high prevalence of *Salmonella* infection in osteomyelitis among SLE patients remains unclear. This may be partly explained by the fact that hypocomplementemia, phagocytosis defect, defective tumor necrosis factor production, increased hemolysis, cellular immune defect, the use of immunosuppressants, incomplete antibiotic use, and glomerulonephritis elicited by SLE can all be deemed to be responsible for disturbances to the elimination process for this intracellular bacteria[4].

Our study revealed that predisposing factors for osteomyelitis in SLE patients include active status of SLE (SLEDAI ≥ 4, 100%), coexistent underlying systemic disease (91%), chronic renal disease (82%), and intensified usage of immunosuppressive agents (82%) — all were compatible with the previously reported predisposing factors for infection in SLE patients[1]. All 11 cases in our study had one or more concurrent infections. This is consistent with the previous report that when infection occurred in SLE patients, one or more concurrent infections were not uncommon[1]. Therefore, concurrent infections should be suspected when osteomyelitis is diagnosed in SLE patients. Laboratory values in our patients indicated either an acute phase reaction that would be expected in an infection, such as elevated CRP (100%) and neutrophilia (55%), or features consistent with active lupus disease.

It is noteworthy that complication occurred frequently, accounting for nearly half of our cases, including motor deficit in 4 cases and death in one. We found that poor prognostic factors responsible for these complications could be: (1) delayed diagnosis and treatment, (2) vertebral involvement, (3) artificial implants in bones, and (4) chronic carrier status. Given that the prognosis for pyogenic vertebral osteomyelitis is reasonably good when it is diagnosed sufficiently early and managed appropriately[15], the poor prognosis of our cases with vertebral osteomyelitis was largely attributable to the significant diagnostic delay. In our study, 3 cases of complicated vertebral osteomyelitis all revealed underlying osteoporosis and some evidence of spinal

Table 2. Clinical characteristics of osteomyelitis in SLE in different studies.

Study	No. of Cases (F/M ratio)	Bone Affected	Cellulitis/ Septic Arthritis	Pathogen	Chronic Renal Disease	Corticosteroid (%)/ Cytotoxic agent (%)	Mortality Rate
Present study	11 (9:2)	Spine 4, tibia 4 femur 2, toe 1	6/3	*Salmonella* 5, *S. aureus* 4, other 2	9	11 (100)/9 (82)	9%
Picillo[2]	1 (1:0)	Femur bilateral	0/1	*S. enteritidis*	1 (100%)	1 (100)/1 (100)	0
Lim[3]	3 (NA)	NA	NA/NA	*Salmonella sp.*	NA	NA/NA	NA
Chen[4]	3 (NA)	NA	NA/3	*Salmonella sp.*	3 (100%)	3 (100)/NA	0
Victorio-Navarra[5]	4 (NA)	Tibia 2, femur 1, radius 1	NA/NA	*M. tuberculosis* 4	NA	NA/NA	0
Gomez Rodriguez[6]	1 (1:0)	Femur	NA/1	*S. enteritidis*	NA	NA/NA	NA
Shahram[7]	3 (3:0)	NA	NA/NA	*Salmonella sp.*	NA	NA/NA	NA
Medina[8]	5 (NA)	NA	NA/5	*Salmonella* A 1, *Salmonella* B 4	4 (80%)	5 (100)/5 (100)	0
Sattar[9]	1 (1:0)	Tibia	0/0	*S. bovis morbificans*	NA	1 (100)/0	0
Smilack[10]	1 (1:0)	Tibia	0/1	*Arizona hinshawii*	NA	1 (100)/0	0
Total of previous study[2-10]	22	Femur 3, tibia 4, radius 1	0/11	*Salmonella sp.* 11, *M. tuberculosis* 4, *Arizona hinshawii* 1	8	11/6	

NA: not available.

compression fracture, which also manifests as nonspecific local pain, resulting in delay of diagnosis and subsequent poor recovery.

We conclude that when patients with SLE, particularly those with active disease, who also suffer chronic renal disease and take intensified immunosuppressive agents, present with local osteoarticular pain, osteomyelitis must be considered seriously. *Salmonella* should be considered as a potential contributing pathogen for long bone osteomyelitis and *S. aureus* should be considered for cases of vertebral osteomyelitis when conducting empirical antimicrobial therapy. The possibility of concurrent infections should be ruled out carefully. Early recognition and treatment is essential to avoid longterm sequelae or even death.

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