The Natural Progression of Adult Elbow Osteonecrosis Related To Corticosteroid Treatment

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Received: 23 January 2012 / Accepted: 7 August 2012 / Published online: 28 August 2012
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Abstract

Background In patients with corticosteroid treatment, the elbow is a rare site of osteonecrosis; there is little information about the rate and risk factors of disease progression in symptomatic and asymptomatic elbows.

Question/Purposes We determined the delay between the beginning of corticosteroid treatment and different stages of osteonecrosis and which stage and dose of steroids influenced disease progression.

Methods Osteonecrosis related to corticosteroids was diagnosed by MRI in 50 elbows of 35 adult patients. Thirty elbows were asymptomatic at initial evaluation (19 with Stage I, 11 with Stage II osteonecrosis). Among the 20 elbows symptomatic at initial evaluation, 13 had radiographic evidence of osteonecrosis without collapse (Stage II) and seven had lesions evident only on MRI (Stage I).

Results At latest followup (average, 17 years; range, 10–25 years), of the 30 previously asymptomatic elbows, pain developed in 24 and collapse occurred in 14; of the 20

previously symptomatic elbows, 15 showed collapse (seven initially with Stage I, eight with Stage II osteonecrosis). The average time between diagnosis and collapse was 8 and 5 years, respectively, for symptomatic elbows with Stages I and II osteonecrosis. Stage at initial visit, development of pain, and continuation of peak doses of corticosteroids were risk factors for disease progression in asymptomatic elbows. In symptomatic elbows, the extent in contact with the articular surface and lesion location were the main risk factors for disease progression.

Conclusions Untreated asymptomatic and symptomatic elbow osteonecrosis related to corticosteroids has a moderate likelihood of elbow collapse, with decrease in ROM, but none of the patients in this case series followed for 10 to 20 years had elbow arthroplasty.

Level of Evidence Level IV, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

In patients undergoing treatment with corticosteroids, the elbow is a rare site of osteonecrosis (ON); there is little information in the literature about the rate and the risk factors of progression of ON in symptomatic and asymptomatic elbows of adult patients when the diagnosis is made at an early stage on MRI or radiographs before collapse. Le et al. [12] provided initial descriptions of atraumatic symptomatic elbow ON in adults and details of the natural course of symptomatic elbows but did not report the natural evolution from asymptomatic Stage I ON.

Our purpose was to define the natural progression of asymptomatic and symptomatic elbow ON from its early stages through long followup (average, 15 years; range, 10–20 years). We hypothesized that stage, presence of

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pain, continuous administration of high doses of corticosteroids, number of lesions in the elbow, location of the lesions [5], and evidence of collapse would influence clinical or radiographic disease progression. Specifically, we intended to assess the clinical and radiographic progression of disease from the beginning of corticosteroid treatment through the different stages of ON and to analyze how the ON stage and presence of pain on presentation predicted the progression of elbow ON. We additionally addressed how the development of articular collapse affected elbow ROM. Finally, we sought to determine how the stage at presentation, continuation of high-dose steroids, and the number of lesions on presentation predicted the progression to collapse.

Patients and Methods

To assess the delay between the beginning of corticosteroid treatment and the different stages of ON, we identified all 638 patients treated between 1985 and 1999 in our institution for hip ON related to corticosteroids. Total-body isotope bone scanning was used to screen for multifocal ON [6] in our hospital in patients in whom hip ON was steroid induced. At the time of implementation of the first MRI in our hospital (1985), MRI could be performed in these patients on the sites of increased uptake on total-body isotope bone scans. MRI was performed on 35 patients to research elbow ON when there was abnormal uptake, and confirmation of the diagnosis of ON was obtained on 50 elbows among the 35 patients. The 35 patients included 16 men and 19 women with a mean age of 29 years (range, 21–50 years) at the time of ON diagnosis. ON was unilateral in 20 patients and bilateral in 15 at the time of the initial examination. The underlying diseases (Table 1) were systemic lupus erythematosus in four patients, ulcerative colitis in five, acute myeloid leukemia in four, acute lymphoblastic leukemia in three, and organ transplantation in 19. The median interval between initiation of corticosteroid treatment and baseline MRI was 19 months (range, 6–24 months). The dosage of corticosteroids was recorded as cumulative, peak (> 200 mg/day), and mean daily methylprednisolone or its equivalent. A conversion

factor of 1/1.25 was used to calculate [3] the methylprednisolone-equivalent dosage of methylprednisolone and prednisolone. The 35 patients with elbow ON received higher ($p = 0.03$) cumulative (mean, 9543 mg) and peak (mean, 427 mg) methylprednisolone-equivalent doses than the 603 patients without elbow ON (means, 4319 mg and 145 mg, respectively). Among the 35 patients, at the time of diagnosis, 14 had stopped corticosteroid treatment, 13 were still receiving steroid treatment but without peak doses, and eight were still receiving treatment with peak doses of corticosteroids. Minimum followup, after inclusion of the patient with elbow ON in the study, was 10 years (average, 15 years; range, 10–20 years). The delay between the beginning of corticosteroid treatment and the diagnosis of ON of the elbow averaged 19 months (range, 9–24 months). With this delay, no elbow had Stage III ON develop.

We made the diagnosis of elbow ON using AP and lateral views of plain radiographs and MRI. AP and lateral radiographs were taken on entry in the study. MR images were obtained with a 0.5-T supraconducting unit from 1985 to 1990 and then with 1.0-T (1990–1998) and 1.5-T (after 1998) supraconducting units. Images were obtained by coronal and sagittal sections. The diagnosis of ON on MRI was based on bandlike abnormal signals and bandlike hypointense zones on T1-weighted images.

ON was graded by the method of Ficat and Arlet [4], modified for the elbow as proposed by Le et al. [12] (Table 2). Collapse of one lesion was the loss of the regularity of the articular surface. When there was difficulty in confirming or inferring collapse on radiographs, a CT scan was performed (36 elbows). We tried to measure the volume of each ON lesion, but because of the small sizes of the lesions, the measurements were not accurate enough to grade each lesion according to volume. However, each elbow could have several lesions with different locations (capitellum, trochlea, radial head, medial or lateral epicondyle). Therefore, rather than the volume of the lesions, we determined the number and location of the lesions for each elbow. To localize the lesion, lesions of the distal humerus and proximal radius and cubitus were classified according to the affected regions: capitellum, trochlea, radial head, medial or lateral epicondyle. The classifications of the 127 lesions of the 50 elbows were lateral epicondyle ($n = 24$ lesions), medial epicondyle ($n = 19$ lesions), capitellum ($n = 35$ lesions), trochlea ($n = 31$ lesions), and radial head ($n = 18$ lesions). All ON of the capitellum, trochlea, and radial head extended to the articular surface. Of the 50 elbows with 127 lesions, three elbows had four lesions, 28 had three lesions, 12 had two lesions, and seven had one lesion. Lesion regression (total disappearance of the abnormal signal) was determined on two different MRIs at 2 and 4 years from the beginning of the study for all

Table 1. Underlying disease ($n = 35$ patients)

Disease	Number of patients
Systemic lupus erythematosus	4
Ulcerative colitis	5
Acute myeloid leukemia	4
Acute lymphoblastic leukemia	3
Organ transplantation	19

patients who had ON diagnosed at entry and who remained asymptomatic or symptomatic without collapse. Patients (with asymptomatic elbows and normal radiographs at the most recent followup) had another MRI at the end of the followup study.

All 35 patients with elbow ON had hip surgery at the time of the first evaluation, and because there was little conclusive evidence of the risk of progression of elbow ON at the beginning of this study, we initiated no specific treatment before the appearance of collapse or intractable pain. Elbows were treated nonoperatively with analgesics and physical therapy to maintain ROM. Thirty elbows with ON were asymptomatic at the time of the initial evaluation and had a total of 58 lesions. Nineteen of these 30 asymptomatic elbows were designated as having Stage I ON and 11 as having Stage II ON at initial evaluation (Table 2). Twenty elbows with ON were symptomatic at the time of the initial evaluation and had a total of 69 lesions. Thirteen of these 20 symptomatic elbows had radiographic evidence of ON without collapse (Stage II) at initial evaluation. The other seven symptomatic elbows had lesions evident only on MRI (Stage I). The mean clinical and radiographic followup was 16 years (range, 10–20 years) for the asymptomatic group and 14 years (range, 10–20 years) for the symptomatic group. All 35 patients had their followup clinical examination and radiographs at the same institution every 6 months until collapse or surgery and then every year until 2010. During the study, no patient was lost to followup, but four of the patients were deceased by the most recent followup. The deaths were related to the underlying disease.

To evaluate the delay and disease progression from the beginning of corticosteroid treatment, we had four end points for survival: pain, changing of stage, collapse, and surgery. Clinical disease progression was defined as (1) development of pain in asymptomatic elbows, (2) loss

of mobility of the joint (3) or performance of surgery to treat intractable pain. Radiographic disease progression was defined as (4) occurrence of new lesions on the same elbow, (5) an advance in stage, or (6) progressive collapse in one or several lesions. We calculated survival curves according to Kaplan-Meier survivorship analysis and compared them using the log-rank test. To construct the life table, the number of elbows at each stage was closely followed and the number of events (pain, changing of stage, collapse, or surgery) was determined for each year. The first year started with the total number of elbows at each stage at the initial visit. When an event occurred, the elbow was registered and the number at risk for the stage was calculated again and so on for each successive year. We performed multivariate analyses using the Cox proportional-hazards model to identify the independent factors regarding radiographic disease progression, clinical disease progression, and failure. The chi-square test was used to analyze differences between two groups of patients (eg, patients with and without continuation of corticosteroid treatment).

Results

The majority of patients showed clinical or radiographic disease progression. In asymptomatic elbows, five of 19 elbows with Stage I ON and nine of the 11 with Stage II ON showed collapse of at least one lesion after the onset of symptoms (Table 2). In symptomatic elbows, disease progression with collapse of at least one lesion was observed in seven of the seven elbows with Stage I ON and eight of the 13 elbows with Stage II ON (Table 2). Collapse always was preceded by pain even when the elbow had several lesions. Three elbows experienced complete resolution of

Table 2. Stage of osteonecrosis at initial visit and latest followup

Stage	Criteria for staging	Number of elbows					
		At initial visit			At final followup		
		Total (n = 50)	Asymptomatic (n = 30)	Symptomatic (n = 20)	Total (n = 50)	Asymptomatic at initial visit (n = 30)	Symptomatic at initial visit (n = 20)
I	Abnormal MRI, normal radiograph	26	19	7	0	0	0
II	Abnormal radiograph but no crescent line	34	11	13	21	16	5
III	Abnormal radiograph with a crescent sign	0	0	0	0	0	0
IV	Collapse of the articular surface without joint space narrowing	0	0	0	21	12	9
V	Joint space narrowing	0	0	0	8	2	6

the ON as documented by MRI within 2 years of diagnosis. No additional cases of resolution were observed between the MRI from the 4-year followup and the MRI from the most recent followup. When progression to pain was observed in asymptomatic elbows, the mean interval between corticoid treatment and symptoms (mild pain) was 7 years (range, 2–12 years) for elbows with Stage I ON and less than 9 years for elbows with Stage II ON. The mean interval between corticoid treatment and collapse was 10 years for Stage I (range, 6–14 years) and 6 years for Stage II (range, 4–10 years), respectively.

There was no loss of elbow mobility before onset of pain or collapse. ROM decreased in flexion and extension after occurrence of collapse. Between occurrence of collapse and most recent followup, the average loss of extension was $15^\circ \pm 9^\circ$ and the average loss of flexion was $12^\circ \pm 6^\circ$. At the most recent followup, 19 of the 29 elbows with collapse deteriorated enough to require surgery with core decompression [11]. No patient underwent an arthroplasty, and no patient believed his or her elbow had deteriorated enough to require surgery for improvement of mobility.

With respect to the factors associated with disease progression in asymptomatic elbows (Table 3), stage at diagnosis ($p = 0.01$) and continuation of peak doses of corticosteroids ($p = 0.04$) were the best predictors of occurrence of pain. Development of pain in the previously asymptomatic elbow was a predictor ($p = 0.02$) of radiographic disease progression to a higher stage or collapse. Collapse was an important ($p = 0.01$) risk factor for decrease of ROM. The number and location of lesions on the elbow were risk factors of radiographic disease progression. When compared using the log-rank test, the Kaplan-Meier survivorship analysis showed elbows with one or two lesions had longer ($p = 0.01$) durations of survival before collapse than elbows with three or four lesions. The location of the lesion also was predictive ($p = 0.03$) of collapse. Only five (16%) of the 31 elbows that had a lesion situated on the trochlea reached the stage of collapse. In contrast, 51% of elbows (18 of 35 elbows) with a lesion situated on the capitellum and 83% (15 of 18 elbows) with a lesion on the radial head had progressed to collapse at most recent followup.

Table 3. Disease progression in asymptomatic elbows

Stage	Continuation of peak doses of corticosteroids	Number of elbows		
		Total	Progression to pain	Progression to collapse
I	Yes	5	5	4
	No	14	5	1
II	Yes	11	11	11
	No	0	0	0

Discussion

In patients with corticosteroid treatment, the elbow is a rare site of ON; there is little information about the rate and risk factors of disease progression in symptomatic and asymptomatic elbows. We therefore evaluated the natural progression of ON related to corticosteroid treatment from its early stages in asymptomatic and symptomatic elbows. We determined the delay between the beginning of the corticosteroid treatment and the different stages of ON and which factors influenced disease progression. We analyzed our hypothesis that stage, occurrence of pain, continuation of peak doses of corticosteroids, number of lesions, and location of the lesion would influence the clinical or radiographic disease progression in the elbow, as has been observed in hip [7] and shoulder [8] ON.

Our study has some limitations. We identified all patients who had ON of the hip and from these patients, we selected the 35 with increased fixation on the elbow with total-body isotope bone scanning and confirmation of diagnosis with MRI. These 35 patients with elbow ON had received higher cumulative and peak methylprednisolone-equivalent doses than the 603 patients with hip ON but without elbow ON, respectively. Therefore, this study population might not be representative of all patients with steroid-related ON of the elbow. However, many patients with high doses of corticosteroids have multifocal ON [10], so we can infer our study reflects the population of patients with elbow ON in terms of simultaneous hip involvement; and we did not observe patients with elbow ON without hip ON during a period of 20 years, as reported by Le et al. [12]. Our number of patients is limited and our study concerns only elbow ON related to steroids. However, except for patients with sickle cell disease or receiving chemotherapy [1], it appears atraumatic elbow ON is always related to steroids, and our series is the largest in terms of patients with early elbow ON. Other limitations are bias attributable to different duration, peak, and cumulative corticosteroid doses, different types of corticosteroids used (even if limited to methylprednisolone and prednisolone), and different routes of administration (intravenous, oral, intramuscular).

Because MRI was performed at the initial evaluation, even for asymptomatic elbows without evident radiographic involvement, analysis of the outcome with continuation of the steroid treatment was possible in this population. Spontaneous total regression was only detected within 4 years after the beginning of the corticoid treatment and is consistent with observations for the hip, knee, or shoulder with corticosteroid-induced ON [2, 7, 8, 17]. However, these series (and our series) concern only a small number of patients and larger series with different doses of corticosteroids are necessary to know the exact incidence

of spontaneous regression of steroid-related ON in the different joints. There was a low incidence of delayed development of other ON lesions in the elbow; only 14 delayed lesions occurred in six elbows for 127 initial lesions in 50 elbows. These new lesions occurred only in patients who received increased peak doses. Therefore, the bone that survives the initial insult might show resistance to repetitive ischemic attacks if the dose is not increased, as observed in the hip or knee [16, 17]. Larger series are necessary to elucidate the exact incidence of expansion of steroid-related ON of the elbow.

The rate of progression of ON to collapse in the elbow of our patients appeared lower than in the hip and shoulder when compared with the data of another study [8] specific to rate of progression of ON in various joints, at least if we accept hip, shoulder, and elbow ON occurred at the same time in the same patients. As reported with other series of hip, knee, or shoulder ON related to corticosteroids [6, 7, 13–15], the rate of disease progression was quicker in symptomatic than in asymptomatic elbows and quicker in elbows with Stage II ON than in elbows with Stage I ON.

We also identified risk factors associated with disease progression. We observed no extension of the number of necrotic lesions for Stage I and II lesions when the steroid administration was continued without peak doses. This conforms to prospective studies using MRI showing the area of the femoral head ON never enlarges during repetitive MRI [9, 16]. The same has been observed for the knee [17] and shoulder [8]. However, we observed new lesions when peak doses with increased levels were received by the patient during the first 2 years after the diagnosis. Spontaneous resolution was observed in early asymptomatic disease (Stage I) under only three conditions: when there was only one lesion on the elbow, when it was situated on the area of the trochlea, and when the patient no longer had peak doses of corticosteroids. Our results in the elbow are consistent with the results of others, suggesting some early hip [9], knee [17], or shoulder [8] lesions may have spontaneous complete or incomplete regression. This situation was a rarity in this series of patients with elbow ON related to high doses of corticosteroids and underlying diseases as compared with the incidence of regression (41%) observed for the knee [17]. Disease progression to collapse was observed in 14 of the 30 asymptomatic elbows and in 15 of the 20 symptomatic elbows. In particular, we found, as in the hip [16] and shoulder [8, 15], an association between the location of the ON and the risk of quick radiographic or clinical failure. No elbow with a symptomatic lesion underwent an arthroplasty in our series.

The time between initiation of steroid treatment and diagnosis of elbow ON was less than 24 months. Spontaneous regression was observed only in asymptomatic patients and within 4 years after the beginning of steroid

treatment. For the other patients, location of the lesion and continuation of peak doses of corticosteroid determined the risk of disease progression. For the majority of patients, asymptomatic or symptomatic ON of the elbow related to corticosteroid treatment should be considered a progressive disease with substantial clinical and radiographic disease progression within a period of 15 years, even if the treatment with corticosteroids has been stopped. However, none of the patients in this series was treated with arthroplasty.

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