
ORIGINAL ARTICLE

Perilesional Sclerosis Associated with Dreaded Black Lines in Incomplete Atypical Femoral Fractures after Antiresorptive Therapy

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ABSTRACT

Introduction: This study aimed to describe the demographic, clinical, and radiological features of sclerosis adjacent to 'dreaded black lines' or radiolucent fracture lines (RFLs) in atypical femoral fractures (AFFs) associated with antiresorptive therapy.

Methods: We reviewed radiographs acquired in our institution in Singapore between 2004 and 2020 from 100 femurs with AFFs, assessing the appearance and location of lesions, and the presence of endosteal or periosteal thickening. Demographic data, type and duration of antiresorptive therapy, and progression to complete fracture or need for prophylactic stabilisation were analysed. The cohort was subdivided into three groups: Group 1A included AFFs with an RFL and perilesional sclerosis; Group 1B included AFFs with an RFL but without perilesional sclerosis; and Group 2 included AFFs without an RFL.

Results: A total of 17 sclerotic RFLs were identified. The majority were non-linear in appearance. Most were located in the subtrochanteric (41.2%) and proximal diaphyseal regions (35.3%), and all were associated with endosteal or periosteal thickening. All sclerotic RFLs occurred in patients with a mean age of 69 years. Sixteen cases (94.1%) had a history of bisphosphonate use, while one case had received denosumab. The mean duration of antiresorptive therapy was 66 months. Three cases (17.6%) progressed to complete fractures and six (35.3%) required prophylactic fixation. No significant differences were observed among the three groups in terms of demographics, antiresorptive therapy, or surgical intervention.

Conclusion: We describe perilesional sclerosis as a previously unrecognised radiological feature adjacent to RFLs in AFFs, with distinctive characteristics. It occurs in approximately one-third of RFLs. Further research is needed to elucidate its pathophysiological and prognostic implications.

Key Words: Bisphosphonates; Femoral fractures; Sclerosis

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Ethics Approval: This research was approved by the SingHealth Centralised Institutional Review Board, Singapore (Ref No.: 2019/2668). The requirement for informed patient consent was waived by the Board as non-identifiable data were used and due to the retrospective nature of the research.

中文摘要

抗骨質吸收治療後不完全性非典型股骨骨折伴隨怪樣黑線周圍硬化

黃啟翔、石佳偉、許鑽美、P Chandra Mohan、方明愛、侯德生、黃勇輝

引言：本研究旨在描述接受抗骨質吸收治療的非典型股骨骨折（atypical femoral fractures, AFF）中，鄰近「怪樣黑線」或透光骨折線（radiolucent fracture lines, RFL）的骨質硬化之人口統計學、臨床及放射學特徵。

方法：我們對2004至2020年間在新加坡我院就診的100例AFF患者之X光片進行回顧性分析，評估病變的形態與位置，以及是否存在骨內膜或骨外膜增厚，同時分析患者的人口統計學資料、抗骨質吸收治療的類型與持續時間，以及是否進展為完全性骨折或需要預防性固定。我們根據影像表現將患者分為三組：1A組為伴有RFL及病灶周圍硬化的AFF；1B組為伴有RFL但無病灶周圍硬化的AFF；2組為無RFL的AFF。

結果：共發現17例硬化性RFL，多呈非線性形態。大多位於股骨大轉子下區（41.2%）及近端骨幹區（35.3%），所有病例均伴隨骨內膜或骨外膜增厚。硬化性RFL患者的平均年齡為69歲，其中16例（94.1%）有雙磷酸鹽使用史，1例曾接受地舒單抗治療。抗骨質吸收治療的平均持續時間為66個月。3例（17.6%）進展為完全性骨折，6例（35.3%）需接受預防性內固定。三組患者在人口統計學特徵、抗骨質吸收治療或手術介入方面均無顯著差異。

結論：我們描述了病灶周圍硬化，此為一種先前未被識別的AFF中RFL附近之放射學特徵，具有獨特的表現形式。其發生率約佔RFL病例的三分之一。需進一步研究以闡明其病理生理機制及預後意義。

INTRODUCTION

Atypical femoral fractures (AFFs) were first recognised as a distinct clinical entity following multiple clinical reports, yet their pathophysiology and clinical characteristics remain incompletely understood.^{1,2} Over time, our understanding of AFFs has evolved, as reflected in ongoing efforts by a task force of the American Society for Bone and Mineral Research (ASBMR) to refine diagnostic criteria.^{1,2} Major features used to define AFFs were first established in 2010 and included fractures following low-energy or no trauma, transverse fractures originating from the lateral cortex which may become oblique medially, complete fractures with a medial spike, and incomplete fractures involving only the lateral cortex, with minimal or no comminution and localised periosteal or endosteal thickening of the lateral cortex.¹ Minor features associated but not required for diagnosis include generalised femoral diaphyseal cortical thickening, unilateral or bilateral prodromal pain in the groin or thigh, incomplete or complete fractures of both femoral diaphyses, and delayed fracture healing.¹ In 2014, new epidemiological studies and clinical data prompted the ASBMR to revise the definition of AFFs,

emphasising their diaphyseal location and requiring at least four of the five major features for diagnosis.² This refined definition provides a more precise framework for identifying AFFs and distinguishing them from typical osteoporotic femoral fractures.² This reflects the dynamic and evolving nature of our understanding of AFFs and highlights that much remains unknown, including the identification of potential novel clinical and radiological features and their implications for patient management.

Radiological studies have also expanded our understanding of AFFs, particularly when Mohan et al³ described multifocal endosteal thickening along the femoral diaphysis in bisphosphonate-related AFFs, highlighting its association with a periosteal beak and/or a 'dreaded black line', also referred to as a radiolucent fracture line (RFL). These features were associated with an increased risk of progression to fracture.³ A subsequent study by Png et al⁴ demonstrated that when an RFL is present, the lesion is likely to persist, either remaining static or progressing to a displaced fracture. The significance of RFLs was also emphasised in the 2015 position statement by the Korean Society for Bone

and Mineral Research, which recommended prophylactic femoral nailing in the presence of an RFL, especially when located in the subtrochanteric region.⁵

Despite these insights, gaps remain in the literature, as not all RFLs progress to complete fractures and there are no clear discerning features to guide when prophylactic fixation is indicated. During our review of patients with AFFs, we observed a previously undescribed radiological feature: perilesional sclerosis—an area of sclerosis closely associated with the presence of an RFL seen in an incomplete AFF. This finding, distinct from previously reported radiological features of AFFs, may have implications for understanding bone stability, fracture progression, and management strategies, as sclerosis has previously been suggested to be associated with fatigue fractures and delayed fracture healing.⁶

Although with established diagnostic criteria and the recognition of RFLs as high-risk markers, it remains unclear why not all RFLs progress to complete fractures or ultimately require intervention. To date, no study has described the presence or significance of perilesional sclerosis in relation to RFLs in AFFs. Our study aimed to address this gap by identifying and characterising this radiological feature in association with RFLs in incomplete AFFs, and by exploring its potential clinical implications.

METHODS

Study Cohort

We retrospectively reviewed plain radiographs of cases of incomplete AFFs in patients presenting to our institution, Singapore General Hospital in Singapore, while receiving bisphosphonate therapy between 2004 and 2020. These cases were retrieved from our institutional AFF registry, which includes patients exhibiting features of AFF that have not yet progressed to a complete fracture.

We reviewed all available plain radiographs of the AFFs, as well as those of the contralateral femur when available. Perilesional sclerosis was defined as a linear area of sclerosis observed on either side of an RFL. All anteroposterior and lateral views were obtained using standard radiographic techniques, and all analysed fractures met the ASBMR criteria for an AFF.^{3,4}

The study cohort of 100 AFFs was subsequently divided into three groups: Group 1A included AFFs with an RFL and perilesional sclerosis; Group 1B included AFFs with

an RFL but without perilesional sclerosis; and Group 2 included AFFs without an RFL.

We also analysed age data and collected information on the type and duration of bisphosphonate therapy. Patients were followed up for sequelae, including progression to complete fracture or subsequent prophylactic fixation. Prophylactic fixation was performed in cases of persistent pain at the site of AFFs, while surgical fixation was performed for patients who progressed to complete fractures.

Image Analysis

All radiographs were reviewed for the presence of RFLs with adjacent sclerosis using Vue Motion (Carestream Health, Rochester [NY], US), and independently assessed by two authors (SBK and TSH), each with over 20 years of clinical orthopaedic experience. RFLs were categorised into one of four patterns: (1) RFL without sclerosis (Figure 1); (2) RFL with linear sclerosis (Figure 2); (3) RFL with patchy continuous sclerosis (Figure 3); and (4) RFL with patchy non-continuous sclerosis (Figure 4).

We recorded the location of each lesion, along with the presence or absence of focal endosteal or periosteal thickening. Cases were followed up until fixation was required or a complete fracture occurred. Lesions were classified as being located in either the subtrochanteric or diaphyseal region, and further subdivided into proximal, middle, or distal thirds. Observations were collected independently by each of the same two authors and correlated. In the event of any discrepancies, a senior radiologist was consulted to provide a final decision.

Statistical Analyses

Pearson's Chi squared test was used to compare categorical data, while one-way analysis of variance was employed to analyse continuous variables. Statistical analyses were performed using SPSS (Windows version 23.0; IBM Corp, Armonk [NY], US). Statistical significance was defined as $p < 0.05$.

RESULTS

There were 100 radiographs of AFFs from 80 cases available for review. Demographic and clinical data of the study cohort are summarised in Table 1. There were 17 femurs in Group 1A, 35 femurs in Group 1B, and 48 femurs in Group 2. All 17 femurs with perilesional sclerosis were independently identified by the two authors previously described. There were no significant differences among the three groups in terms of patient

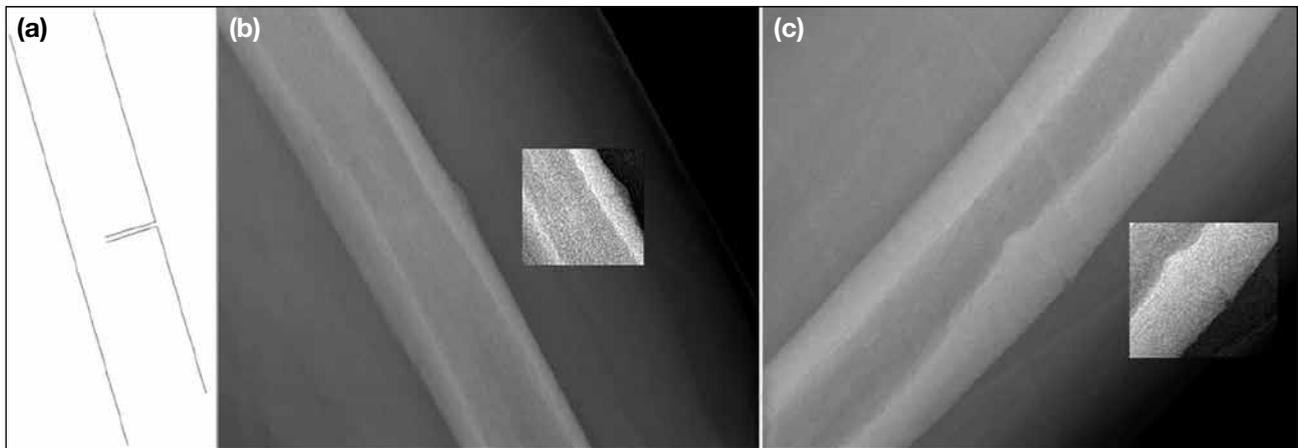


Figure 1. (a) Illustration of radiolucent fracture line (RFL) without sclerosis. (b) Anteroposterior and (c) lateral radiographs of the left femur showing an RFL without sclerosis.

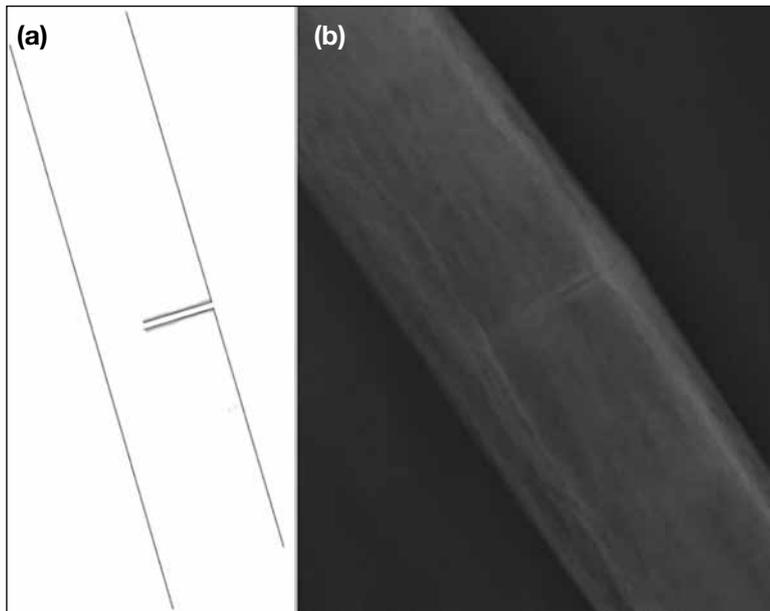


Figure 2. (a) Illustration of radiolucent fracture line (RFL) showing linear sclerosis. (b) Lateral radiograph of the left femur showing an RFL with linear sclerosis.

demographics (age: $p = 0.979$); the patients were predominantly female and Asian. All had a history of bisphosphonate use, except for two AFF cases with a history of denosumab use only (one in Group 1A and one in Group 2). There were no significant differences in the duration of antiresorptive therapy ($p = 0.418$), progression to complete fracture ($p = 0.078$), or subsequent prophylactic fixation ($p = 0.076$) among the three groups. The radiographic finding of perilesional sclerosis was observed in 17 of the 100 femurs (17%), with bilateral involvement in three patients who were all female with a mean age of 66 years; two were Chinese

(88.2%) and the remaining patient was of Indian descent. The mean (\pm standard deviation) duration of bisphosphonate use was 66 ± 31 months (range, 4-120). Only one femur in Group 1A was from a patient with a history of denosumab use without prior bisphosphonate therapy. Bisphosphonate treatment was discontinued upon diagnosis of AFF in all patients. Three femurs (17.6%) subsequently progressed to complete fractures, while six incomplete fractures required prophylactic fixation (35.3%). The mean time to surgical fixation or prophylactic fixation from the date of presentation with perilesional sclerosis was 9 ± 12 months.

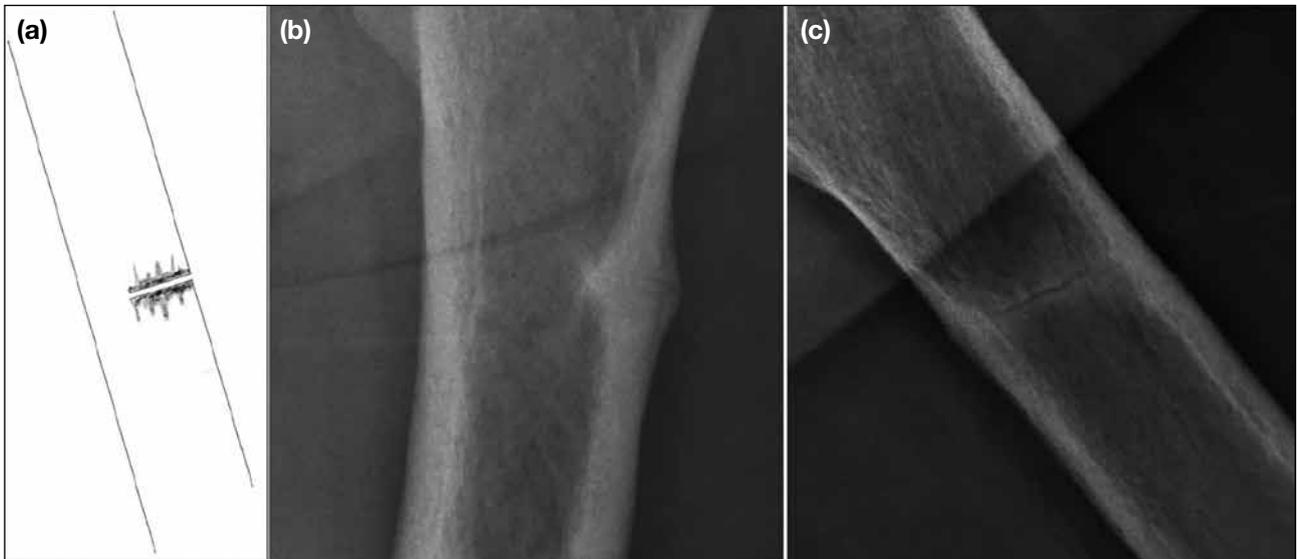


Figure 3. (a) Illustration of radiolucent fracture line (RFL) with patchy continuous sclerosis. (b) Anteroposterior and (c) lateral radiographs of the left femur showing an RFL with patchy continuous sclerosis.

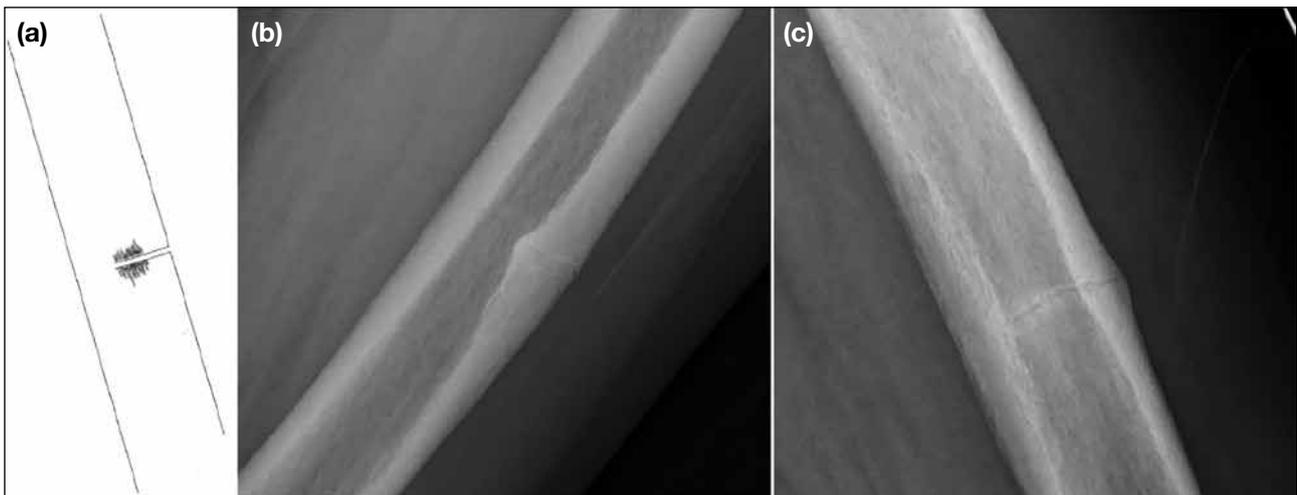


Figure 4. (a) Illustration of radiolucent fracture line (RFL) with patchy non-continuous sclerosis. (b) Anteroposterior and (c) lateral radiographs of the left femur of the same patient in Figure 2 showing RFL with patchy non-continuous sclerosis.

Table 1. Clinical data of the study cohort (n = 100).*

	Incomplete AFFs with RFLs		Incomplete AFFs without RFLs	p Value
	Group 1A (n = 17)	Group 1B (n = 35)	Group 2 (n = 48)	
Perilesional sclerosis	17 (100%)	0	0	N/A
Age, y	69 ± 11	69 ± 10	69 ± 11	0.979
Female sex	17 (100%)	34 (97.1%)	47 (97.9%)	0.787
History of bisphosphonate therapy	16 (94.1%)	35 (100%)	47 (97.9%)	0.364
Duration of antiresorptive therapy, mo	66 ± 31	51 ± 45	58 ± 33	0.418
Progression to complete fracture	3 (17.6%)	13 (37.1%)	8 (16.7%)	0.078
Prophylactic fixation	6 (35.3%)	10 (28.6%)	6 (12.5%)	0.076

Abbreviations: AFF = atypical femoral fracture; N/A = not applicable; RFL = radiolucent fracture line.

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified.

Table 2. Radiographic features of perilesional sclerosis (n = 17).

	No. (%)
Non-linear	16 (94.1%)
Non-continuous	10 (58.8%)
Seen on lateral view	15 (88.2%)
Seen on anteroposterior view	9 (52.9%)
Presence of endosteal or periosteal thickening	17 (100%)

The radiographic features of perilesional sclerosis in Group 1A are summarised in Table 2. Each sclerotic lesion was observed in an incomplete AFF and only in the presence of an RFL. Perilesional sclerosis was identified on lateral views in 15 femurs (88.2%), while only nine femurs (52.9%) demonstrated sclerosis on anteroposterior views. The lesions were mainly located in the subtrochanteric region (n = 7, 41.2%), followed by the proximal diaphyseal region (n = 6, 35.3%) and the mid-diaphyseal region (n = 4, 23.5%). All lesions were associated with either adjacent endosteal thickening or periosteal thickening. Of the 17 lesions with perilesional sclerosis, 16 (94.1%) were RFLs with patchy sclerosis of varying widths along either side of the fracture line, and 10 (58.8%) demonstrated patchy non-continuous sclerosis.

Among the 17 femurs with sclerotic RFLs, three had earlier radiographs (mean, 56.4 months; range, 0.5-96.3) showing an RFL without adjacent sclerosis, indicating that perilesional sclerosis developed later. Once sclerosis appeared, it persisted in all subsequent follow-up radiographs. For the eight femurs that did not undergo surgery, the mean duration between the first presentation of RFL with perilesional sclerosis and the last available radiograph was 31 ± 22 months (range, 0-57.6). Follow-up was achieved for 100% of the 17 lesions, with a mean follow-up duration of 72 ± 45 months (range, 8-184). Regarding inter-observer variability, there was complete agreement between both readers on the presence and pattern of sclerosis.

DISCUSSION

Our study describes the presence of perilesional sclerosis adjacent to the RFL, previously described by Png et al,⁴ and the radiological progression of AFFs in which the RFL is recognised as the penultimate radiological feature before progression to a complete fracture. We observed that an RFL can be associated with, or may later develop, perilesional sclerosis. This radiological feature has not previously been documented in AFFs, which are predominantly located between the subtrochanteric

region and mid-diaphyseal regions of the femur, may be bilateral and are consistently associated with endosteal or periosteal thickening. In our study, perilesional sclerosis appears to occur in approximately one-third of AFFs with an RFL, and is usually seen on lateral radiographic views, and occasionally on anteroposterior radiographic views. While the variability in its appearance and its significance remain largely unstudied, and descriptions in the literature are scarce, our study presents observations that may enhance our understanding of this entity.

AFFs are considered to be 'tensional' stress fractures, typically initiating along the upper two-thirds of the lateral femoral shaft corresponding to regions subjected to greater tensional forces.⁷ Accordingly, RFLs are better observed as linear structures across the femoral diaphysis on lateral views. As perilesional sclerosis appears to occur in association with RFLs, this may account for its notably high prevalence on lateral views of the femoral shaft.

In the majority of our cases, perilesional sclerosis was observed only on the lateral views. In two cases with both anterior and lateral cortical thickening, sclerosis was visible on both anteroposterior and lateral views. These findings suggest that, in most cases, perilesional sclerosis may be related to viewing cortical thickening at right angles to its long axis. However, in two cases, perilesional sclerosis was seen on the anteroposterior views despite cortical thickening being confined to the lateral cortex. This suggests that, in these cases, there was focal sclerosis at the intracortical fracture margins.

Radiologically, sclerosis at fracture sites has been described as a feature of fracture non-union.⁸ Although sclerosis has been postulated to be associated with avascular necrosis or reduced metabolic bone activity,⁹ it has also been linked to prolonged time to union.¹⁰ Perilesional sclerosis has been mentioned in some cases of insufficiency fractures but is rarely described in AFFs. Only a single study by McKenna et al¹¹ described sclerosis in relation to AFFs, but only on computed tomography scans without specific reference to its relationship with RFLs. The fact that this feature is observed only in a subset of incomplete AFFs with variable continuity along the RFL, suggests that it may represent a phase in the pathophysiological progression of AFFs.

Perilesional sclerosis associated with cortical thickening may resemble that seen in stress or fatigue fractures.

However, cases with intracortical perilesional sclerosis may represent an early phase of the process leading to non-union. Fracture non-union is usually associated with sclerosis at the fracture margins, and the two cases in our cohort where sclerosis was confined to the lateral cortex may represent non-union of the incomplete fracture, akin to hypertrophic non-union involving the lateral cortex. This may be the result of persistent tensile stresses that inhibit bony union.¹² These lesions also appeared to progress from an isolated RFL to an RFL with adjacent sclerosis, with this radiographic feature persisting for a mean duration of 31 ± 22 months. Perilesional sclerosis may take considerable time to develop but can persist long after initial presentation. We postulate that it could represent the development of a chronic non-union state in incomplete AFFs. Bisphosphonates such as alendronate are known to have prolonged effects on osteoclast function, and these may continue long after cessation of therapy.¹³

Although there were no significant differences in the proportion of cases that progressed to complete fracture or required prophylactic fixation between Group 1A and Group 1B, a higher rate of surgical fixation in Group 1B was noted (65.7% vs. 52.9%). A histological study by Schilcher et al¹⁴ demonstrated signs of attempted healing at the site of AFFs; however, the current literature does not explain the pathological differences between AFFs that eventually heal and those that do not. Future histological studies could examine samples of perilesional sclerosis to explore the underlying pathology and provide insights into its clinical significance.

Strengths and Limitations

A strength of this study is the 100% follow-up rate over a mid-term duration for a previously undescribed radiological finding in AFFs. The main limitation is the limited sample size of patients with perilesional sclerosis, although this may reflect the low prevalence of AFFs among patients on antiresorptive therapy. Additionally, the predominance of female patients in the cohort limited our ability to assess potential gender-related differences. Another limitation is the irregular follow-up of patients due to variation in individual physicians' clinical practices and the retrospective nature of the study. Longer-term, regularly scheduled follow-up with standardised radiographic imaging should be considered in future studies to better evaluate the relationship between these lesions and fracture outcomes.

CONCLUSION

We describe perilesional sclerosis as a previously unrecognised radiological feature along the RFL, in incomplete AFFs with distinctive characteristics. Its presence may suggest a state of non-union and was observed in approximately one-third of cases with an RFL. Further research involving larger cohorts could shed light on its pathophysiological and prognostic significance.

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