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The Clinical Utility of MRI in Evaluating for Osteomyelitis in Patients Presenting with Uncomplicated Cellulitis

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ABSTRACT

Magnetic resonance imaging (MRI) is vital in the diagnosis of osteomyelitis (OM) in patients presenting with cellulitis. Typically, cellulitis is treated with oral antibiotics; however, patients with concomitant OM may require long-term intravenous antibiotics or surgical intervention. We reviewed lower extremity MRIs in patients presenting with cellulitis and clinical concern for OM. We found 488 patient examinations spanning 5 years (2011 to 2016); 47 patients were excluded (final N = 441). Each MRI was interpreted by a radiologist to determine the rate of OM, abscess, ulceration, and imaging diagnosis of cellulitis. Concurrent assessment of the electronic medical record was performed to review patient demographics, the presence of abscess and/or ulceration, and comorbidities such as diabetes, hyperlipidemia (HLD), atherosclerotic disease, and peripheral vascular disease. Of the 441 lower extremity MRIs included, 170 (39%) were diagnosed with OM, 236 (54%) had ulcers, and 66 (15%) had abscesses. Age, laterality, and reporting physician were not statistically significant independent variables in the rate of reported OM. Diabetes and HLD/atherosclerotic disease were both statistically significant variables with regard to OM rates. Clinical documentation and MRI diagnosis of ulceration were both statistically significant variables in the rate of OM. Regression analysis determined that body part, ulceration, HLD/atherosclerosis, and sex were independent predictors of OM. In our study, of the population of patients with a high clinical suspicion for OM, 39% had OM diagnosed on MRI. However, the incidence of OM in uncomplicated cellulitis was only 11.8% compared with 43.9% in complicated cellulitis. When considering the forefoot alone, patients with ulceration at MRI were 5.6 times more likely to have underlying OM than those without.

Cellulitis, a soft tissue infection involving the skin and subcutaneous tissues, is a common reason for hospital admission (1–3). It is a clinical diagnosis characterized by soft tissue swelling, erythema, and warmth of the affected area, often with an ill-defined margin separating it from the adjacent uninvolved skin (1–6). Adult osteomyelitis (OM) is an infection of bone in which >90% of cases are a result of contiguous spread from nearby skin due to trauma, surgery, or diabetic ulceration (1,2,7–9). OM may be a comorbidity accompanying cellulitis. The clinical symptoms of OM can be nonspecific, thereby making its diagnosis challenging.

Cellulitis is typically treated with oral antibiotics, whereas OM treatment requires long-term intravenous antibiotics. As a result, appropriate clinical management depends heavily on imaging evaluation to confirm or exclude the presence of OM in the setting of cellulitis. Despite its ubiquity, radiographs are of limited utility in the evaluation of early OM. Magnetic resonance imaging (MRI) provides better diagnostic information for the diagnosis of OM than other imaging modalities and is often the confirmatory test of choice.

Our primary aim was to define the rate of OM in patients presenting with cellulitis. Our secondary aim was to assess the associations of OM with other factors such as comorbid conditions, age, infection location, and sex. We also sought to demonstrate the incidence of OM in uncomplicated cellulitis compared with complicated cellulitis as defined by the presence of abscess, ulceration, or other medical comorbidities such as diabetes, hyperlipidemia (HLD), and peripheral vascular disease (PVD). As such, we reviewed those patients who underwent MRI for evaluation of clinically suspected OM. We hypothesized that the incidence of OM in uncomplicated cellulitis is lower than that in cellulitis complicated by ulceration or abscess.

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Methods

After gaining institutional review board approval, we used a computer search engine to review all patients from our institution with an MRI of either lower extremity (from knee to forefoot) over a 5-year period (January 1, 2011, to December 31, 2016) with a clinical suspicion of OM in the setting of cellulitis. This included those patients with documented history of cellulitis in the medical record or on the indication for imaging. Only adult patients (aged ≥18 years) were included in this study. Typically, these patients had soft tissue infection or ulceration. The search resulted in 488 MRI examinations for review. Exclusion criteria included recent surgical manipulation (within the last 6 weeks), surgical hardware at the site of interest (regardless of hardware age), and examinations ordered to follow a prior MRI diagnosis of OM. One study was excluded because it was deemed nondiagnostic at the time of interpretation. In total, 47 patients were excluded. This resulted in 441 individual patients included in our analysis.

MRI studies were interpreted by 1 of 7 board-certified radiologists with multiple years of experience in musculoskeletal imaging. All of the studies were reviewed in the clinical setting, and radiology reports were produced for each study. These reports were retrospectively reviewed, specifically looking for the presence or absence of OM, abscess, ulceration, and/or cellulitis. Equivocal cases of OM and cellulitis were resolved by consensus at the time of secondary review. Demographic information collected from the electronic medical record (EMR) included age, sex, and diagnosis of diabetes, HLD/atherosclerotic disease, and/or PVD. Additionally, physical examination findings were documented, including the presence or absence of skin ulcerations, wounds, and cellulitis/skin infection (secondary signs of OM) (Table 1). This study did not, however, distinguish the timing of chart data for patients with multiple visits to the institution. For example, if a patient had a history of skin ulceration on a prior clinical visit, that variable was marked positive at imaging whether or not they had ulceration at the time the MRI was performed. Additionally, some demographic data was not available within our EMR owing to incomplete or absent records, especially in the instance of outpatient referrals. Information from a thorough history and physical examination was not available in these cases.

Using the demographic data and physical examination data from the medical charts along with the MRI findings, univariable analyses were conducted to identify factors that might be associated with OM. The chi-squared test or Fisher's exact test (as appropriate) was used for categorical variables, and the *t* test was used for age, the only continuous variable of interest. A multivariable analysis based on a logistic regression model was carried out to determine which factors were associated with OM, when all proposed factors were considered simultaneously.

A secondary imaging review was then conducted to verify the diagnostic accuracy of skin ulceration at MRI. This included a retrospective review of 100 of the 441 included MRI studies. These 100 studies were chosen at random, irrespective of clinical data. The presence or absence of ulceration at retrospective review was compared with original reports to determine the rate at which ulcerations may be present but not reported. Unless otherwise specified, a result was considered statistically significant at $p < .05$. All analyses were performed using SAS version 9.4 (SAS Institute).

Results

Of the 441 included cases, 170 (38.5%) established a diagnosis of OM on the basis of the MRI findings. 236 (53.5%) had demonstrable ulceration on MRI at initial review, 66 (15.0%) had an abscess, and 307 (91.1% of 337) had the diagnosis of cellulitis by MRI (Table 2). Some of the MRI reports had equivocal findings when it came to reporting abscesses. This included findings of fluid collection on a noncontrast MRI where evaluation of enhancement was not available. In these cases, it was assumed that if no explicit mention of an abscess was made in a report, that particular study was negative for abscess. However, the same was not assumed for cellulitis. Many times, the indication for the study was simply "cellulitis." Therefore, some MRI reports did not emphasize MRI findings of cellulitis even when they were positive at imaging, as a clinical diagnosis of cellulitis was known. Therefore, the cellulitis results from nearly a quarter of the MRI reports were not explicitly mentioned and therefore are documented as unknown.

On EMR review, we found that 3.2% of the 441 included cases had type 1 diabetes, and 54.0% had type 2 diabetes. 43.3% had HLD or atherosclerotic disease, and 24.4% had PVD. All 4 of the above risk factors have a missing data rate of 7% to 8% (Table 3).

When separating the 441 cases into those with MRI findings of OM (170) and those without (271), there was no statistical difference for variables such as age ($p = .40$), laterality ($p = .69$), reporting physician ($p = .14$), or patient class (outpatient or inpatient/emergency) ($p = .19$) (Table 4). However, there was a statistically significant difference in regard to sex, with OM more frequent in males (45%) than females (27%) ($p = .0003$).

Table 1
Patient demographics (N = 441)

Characteristic	Value
Sex	
Male	289 (66)
Female	152 (34)
Age (yr)	62 (24 to 98)
Associated conditions	
Diabetes, type 1	13 (3)
Diabetes, type 2	221 (54)
Hyperlipidemia/atherosclerosis	175 (43)
Peripheral vascular disease	99 (24)
Physical examination findings	
Cellulitis/subcutaneous infection	396 (94)
Skin ulcer/wound	281 (69)
Patient class	
Inpatient/emergency department	391 (89)
Outpatient	50 (11)

Data are n (%) or mean (range).

Table 2
Magnetic resonance imaging findings

Finding	Number
Osteomyelitis	
Positive	170 (39)
Negative	271 (61)
Equivocal/unknown	0
Ulceration	
Positive	236 (54)
Negative	205 (46)
Equivocal/unknown	0
Abscess	
Positive	66 (15)
Negative	357 (81)
Equivocal/unknown	18 (4)
Cellulitis	
Positive	307 (70)
Negative	30 (7)
Equivocal/unknown	104 (24)

Data are n (%).

Table 3
Electronic medical record review findings

Number	Value
Diabetes mellitus type 1	
Positive	13 (3)
Negative	395 (90)
Missing data	33 (7)
Diabetes mellitus type 2	
Positive	221 (50)
Negative	188 (43)
Missing data	32 (7)
Hyperlipidemia/atherosclerosis	
Positive	175 (40)
Negative	229 (52)
Missing data	37 (8)
Peripheral vascular disease	
Positive	99 (22)
Negative	306 (69)
Missing data	36 (8)
Cellulitis	
Positive	396 (90)
Negative	25 (6)
Missing data	20 (5)
Ulcer/wound	
Positive	281 (64)
Negative	127 (29)
Missing data	33 (7)

Data are n (%).

Table 4
Incidence of osteomyelitis adjusted for risk factors

Variable	All Patients	Positive for Osteomyelitis	Negative for Osteomyelitis	*p* Value
Age (yr)	62.0 (15.4)	62.8 (13.6)	61.6 (16.4)	.40
Body part				<.0001
Knee	9	1 (11)	8 (89)	
Ankle/hindfoot	72	18 (25)	54 (75)	
Forefoot	233	124 (53)	109 (47)	
Other*	127	27 (21)	100 (79)	
Sex				.0003
Female	152	41 (27)	111 (73)	
Male	289	129 (45)	160 (55)	
Diabetes type 1†				.03
Positive	13	9 (69)	4 (31)	
Negative	395	154 (39)	241 (61)	
Diabetes type 2†				<.0001
Positive	221	110 (50)	111 (50)	
Negative	188	53 (28)	135 (72)	
Diabetes type 1 or 2†				<.0001
Positive	234	119 (51)	115 (49)	
Negative	175	44 (25)	131 (75)	
Hyperlipidemia/atherosclerosis†				.001
Positive	175	86 (49)	89 (51)	
Negative	229	76 (33)	153 (67)	
Peripheral vascular disease†				.79
Positive	99	41 (41)	58 (59)	
Negative	306	122 (40)	184 (60)	
Ulcer by chart†				.0004
Positive	281	127 (45)	154 (55)	
Negative	127	34 (27)	93 (73)	
Cellulitis by chart†				.23
Positive	396	159 (40)	237 (60)	
Negative	25	7 (28)	18 (72)	
Ulcer by MRI				<.0001
Positive	236	126 (53)	110 (47)	
Negative	205	44 (21)	161 (79)	
Cellulitis by MRI‡				.03
Positive	307	112 (36)	195 (64)	
Negative	30	5 (17)	25 (83)	
Laterality				.69
Right	225	89 (40)	136 (60)	
Left	215	81 (38)	134 (62)	
Patient class				.19
Inpatient/ED	391	155 (40)	236 (60)	
Outpatient	50	15 (30)	35 (70)	
Reporting physician				.14
1	320	123 (38)	197 (62)	
2	32	14 (44)	18 (56)	
3	28	6 (21)	22 (79)	
4	42	21 (50)	21 (50)	
5	17	5 (29)	12 (71)	
6	1	1 (100)	0	
7	1	0	1 (100)	

Data are mean (standard deviation) or n (%).
* Elsewhere besides the knee, ankle/hindfoot, and forefoot.
† 5% to 8% of data sets are incomplete across all patients.
‡ 24% of data sets are incomplete across all patients.
Abbreviation: ED, emergency department; MRI, magnetic resonance imaging.

Only 13 of the 441 cases had type 1 diabetes. However, there was still a statistically significant difference in rates of OM, with a higher rate in patients with type 1 diabetes ($p = .03$). 221 cases had type 2 diabetes, and there was a statistically significant increase in the rate of OM in patients with type 2 diabetes (49.8%) versus those without (28.2%) ($p < .0001$). When combining type 1 and type 2 diabetes into a single risk factor, there was a statistically significant increase in the rate of OM in patients with diabetes (50.9%) versus those without (25.1%) ($p < .0001$).

When obtaining data from the EMR, HLD and atherosclerotic disease were combined into 1 category for this study. There was a statistically significant difference in rates of OM in patients with HLD/atherosclerotic disease (49.1%) versus those without (33.2%) ($p = .001$). We expected similar findings when comparing those with PVD; however, no significant difference in the rates of OM could be found in patients with documented PVD (41.4%) versus those without (39.9%) ($p = .79$).

Both skin ulcerations and cellulitis are considered risk factors for OM and pertinent findings on MRI. We found that the presence of either variable was higher at EMR review than at MRI. For ulceration, 68.9% of cases were positive by EMR review, whereas only 53.5% were positive at MRI. For cellulitis, 94.1% were positive by EMR review and 91.1% were positive at MRI. There was a statistically significant increased rate of OM in patients with ulceration at EMR review (45.2%) versus those without (26.8%) ($p = .0004$). No significant difference in the rates of OM were found in patients with cellulitis at EMR review (40.2%) versus those without (28.0%) ($p = .23$). However, a higher rate of OM was found

Table 5
Osteomyelitis (OM) rate in complicated versus uncomplicated cellulitis

Cellulitis	Total	OM Positive	OM Negative
Uncomplicated	34 (8.3)	4 (11.8)	30 (88.2)
Complicated*	237 (53.7)	104 (43.9)	133 (56.1)

Data are n (%).
* Complicated cellulitis is defined by the presence of ≥1 of the following variables: ulceration, abscess, diabetes (type 1 or 2), peripheral vascular disease, or hyperlipidemia/atherosclerosis.

in patients with a cellulitis diagnosis at MRI (36.5%) versus those without (16.7%) ($p = .03$). There was also a higher rate of OM in patients with ulceration at MRI (53.4%) versus those without (21.5%) ($p < .0001$).

Variables included for multivariate analysis included age, sex, diabetes, body part, HLD/atherosclerosis, PVD, ulcer by MRI, patient class (inpatient versus outpatient), laterality, cellulitis by chart, and abscess. In the final logistical regression model, body part ($p < .0001$), ulcer ($p < .0001$), HLD/atherosclerosis ($p = .005$), and sex ($p = 0.008$) were significantly associated with OM. Additionally, none of the pairwise interactions between selected variables was found to be statistically significant. Therefore, multivariable analysis of the data determined that body part, ulceration, HLD/atherosclerosis, and sex were significant predictors of OM.

Only 34 (8.3%) of the 441 patients were found to have uncomplicated cellulitis, which we defined as cellulitis in the absence of any of the following 6 variables: ulceration, abscess, diabetes (type 1 or 2), PVD, or HLD/atherosclerosis (Table 5). Of those 34 patients, only 4 (11.8%) were found to have underlying OM at MRI; the remaining 30 (88.2%) were negative for OM. This is in contrast to 237 (53.7%) patients who were found to have complicated cellulitis. Of these, 104 (43.9%) also carried a diagnosis of OM at MRI. When referencing only the forefoot, the presence of an ulcer at MRI was associated with a 5.6 times greater likelihood of OM than those without ulceration (Table 6).

Of the 100 studies randomly selected for retrospective ulcer review, 5 (5%) had skin ulceration deemed grade 2 or higher that was not reported at the time of dictation. Of these 5 cases, 3 (60%) were reported as "skin irregularity" and compatible with early grade 2 ulceration; 1 case was definitively present but not reported; and the last case was subtle but agreed to be present after consensus review.

Discussion

The majority of cases of OM are complicated by adjacent skin ulceration, soft tissue abscess, and sinus tract (8,10). If an ulcer is present, the risk of OM is quite high, and even higher if ulceration extends to the underlying bone and measures >2 × 2 cm (11–13). In the presence of soft tissue swelling but no ulcer, OM is unlikely to be present (13). When an ulcer is present, the physical exam can be supplemented with the probe to bone test, in which a sterile probe is inserted into an ulcerated lesion. If the probe comes to a hard stop it is considered positive. This test has a positive predictive value for OM of 57% and a negative predictive value of 91% (12,14,15).

Prompt diagnosis of OM is imperative, because it may require long-term intravenous antibiotic treatment or surgical removal of the infected bone. To date, there is little evidence to suggest that OM exists in the setting of uncomplicated cellulitis. In an effort to shed light on the incidence of OM in uncomplicated cellulitis and the utility of advanced imaging in these cases, we reviewed and evaluated MRIs of the lower extremity in a cohort of consecutive patients over a period of 5 years (2011 to 2016).

OM in adults frequently involves digits of the feet and is often associated with predisposing conditions such as diabetes or PVD. These comorbidities produce a constellation of factors that ultimately increase abnormal pressure on the foot. This leads to ulcerations and infections that are worsened in the setting of impaired wound healing (3,10). Individuals with diabetes have a 25% lifetime risk of developing a foot complication, and 15% of those will develop a skin ulceration; 1 in 5 of these will progress to OM (9,12,14,16). When comparing patients with and without diabetes, we found a statistically significant increase in the rate of OM in patients with diabetes. Interestingly, there was no difference in the incidence of OM in patients with PVD versus those without. Patient age or the presence of abscess did not appear to be strong factors associated with OM. However, multivariable analysis demonstrates that HLD, ulceration, body part, and sex are all independent predictors of OM. When limiting the analysis to the forefoot, we found that patients with ulcerations were 5.6 times more likely to have underlying

Table 6
Osteomyelitis odds ratio estimates

Compared variables	Odds Ratio	95% Confidence Limits	
Ankle/hindfoot versus forefoot	0.292	0.146	0.585
Knee versus forefoot	0.203	0.023	1.773
Other* versus forefoot	0.231	0.131	0.405
Male versus female	1.963	1.189	3.241
Hyperlipidemia/atherosclerosis (presence versus absence)	1.951	1.226	3.103
Ulceration on magnetic resonance imaging (presence versus absence)	5.581	3.422	9.101

* Elsewhere besides the knee, ankle/hindfoot, and forefoot.

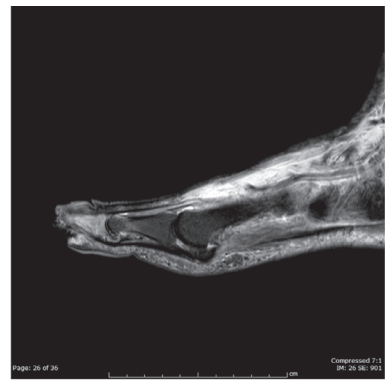
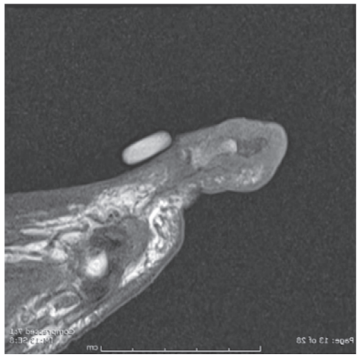
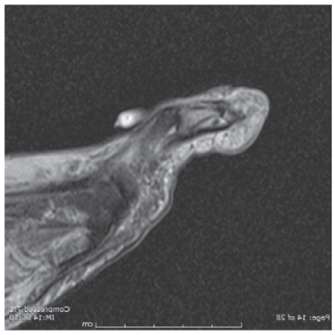


Fig. 1. Normal marrow signal of the distal phalanx is replaced by hyperintensity on short-TI inversion recovery (STIR) imaging (*A*) and hypointensity on T1 (*B*). Additionally, there is mild increased edema-like signal in the adjacent subcutaneous issues and an overlying ulceration extending to the phalanx. These findings represent complicated cellulitis and concurrent osteomyelitis.



A) Sagittal non contrast T1 weighted image of the second toe



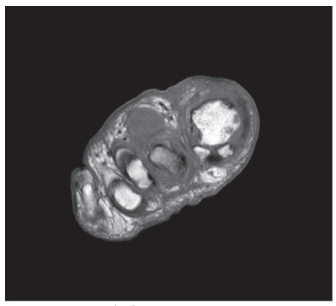
B) Sagittal STIR image of the second toe

Fig. 2. Normal marrow signal of the distal phalanx is replaced by hypointense signal on T1 (*A*) and hyperintensity on short-TI inversion recovery (STIR) imaging (*B*). Edema-like signal is present in the surrounding soft tissue. In the absence of adjacent ulceration and or abscess, these findings represent uncomplicated cellulitis and concurrent osteomyelitis.

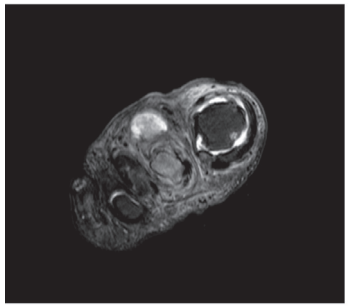
OM than those without. In regard to location, those with forefoot ulcerations were 4 times more likely to have OM than anywhere else in the lower extremity. Finally, we found that men were overall 1.7 times more likely to have OM than women.

Diagnostic imaging options used for the evaluation of lower extremity OM include plain radiography and MRI. Hallmark signs on radiographs of OM include soft tissue swelling, osteolysis, periosteal reaction, and bone destruction (13,17). Although plain radiography has a lag time of approximately 10 to 21 days before OM becomes apparent, it is currently the preferred initial imaging modality since it is readily available and inexpensive and provides adequate resolution of osseous structures (2,10,18). Under the current Infectious Diseases Society of America guidelines, when a diagnosis of OM is uncertain, repeat radiographs after 2 to 4 weeks of treatment is recommended rather than proceeding directly to advanced imaging (13).

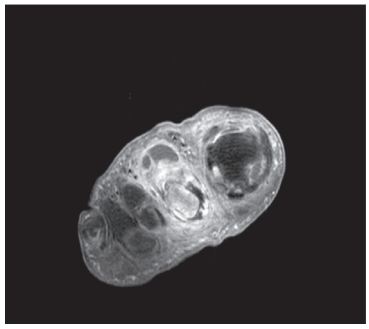
MRI is the advanced imaging modality of choice, as it has been shown to be the most useful and reliable imaging study in the early detection of OM. Existing literature supports an MRI sensitivity of 92% and specificity of 86% in the detection of OM, the highest of any imaging modality (2,7,11,17). Primary signs of OM include decreased marrow signal intensity on T1-weighted images and increased marrow signal intensity on T2-weighted images (Figs. 1 and 2), with marrow enhancement after gadolinium administration (Fig. 3) (7,17). Secondary MRI features that suggest OM are cellulitis, phlegmon, adjacent soft tissue ulcers, and cortical bone destruction (17). Cellulitis on MRI shows thickening of subcutaneous tissues with ill-defined increased signal intensity of superficial soft tissues on T2-weighted sequences and corresponding low signal intensity on T1-weighted sequences (1,7,12). Although MRI is increasingly performed to evaluate for potential bone infection, diagnosis of OM in the foot may be confounded by signal changes from acute Charcot arthropathy, fractures, and postoperative changes,



A) Short axis T1



B) Short axis STIR



C) Short axis T1 with fat suppression after administration of contrast

Fig. 3. Postcontrast images depict a rim-enhancing fluid collection (abscess) dorsal to the second metatarsal. The second metatarsal marrow is replaced by T1 signal hypointensity and short-TI inversion recovery (STIR) imaging hyperintensity. Postcontrast images depict corresponding enhancement. Findings are consistent with complicated cellulitis and concurrent osteomyelitis.

reinforcing the importance of a comprehensive history, physical examination, and correlative laboratory testing (8,9).

Even though advanced imaging studies can be helpful when diagnosing OM, the preferred diagnostic criteria for OM are a positive bone culture and histopathology that is consistent with necrosis (9,10,15,17). This test is more invasive and is frequently bypassed in the presence of positive imaging studies with a high clinical index of suspicion. As such, Al-Khawari et al (18) evaluated the capability of MRI to adequately depict and characterize the changes seen in diabetic foot infections. They looked at 29 diabetic patients with suspected foot infections and compared the MRI findings to subsequent clinical or histopathological findings. They found that of the 14 OM cases diagnosed by MRI, there was biopsy-proven OM in only 11 and concluded that MRI and histological diagnosis were in concordance 79% of the time. The positive and negative predictive value in their study was 79% and 100% respectively (18). Although our study does not focus on histopathologic findings compared with MRI results, the Al-Khawari et al study (18) found that MRI overestimates the number of OM cases. This is to say that MRI testing should be done in patients with high suspicion of having OM and not everyone. In our study, we found an 11.8% rate of OM in patients

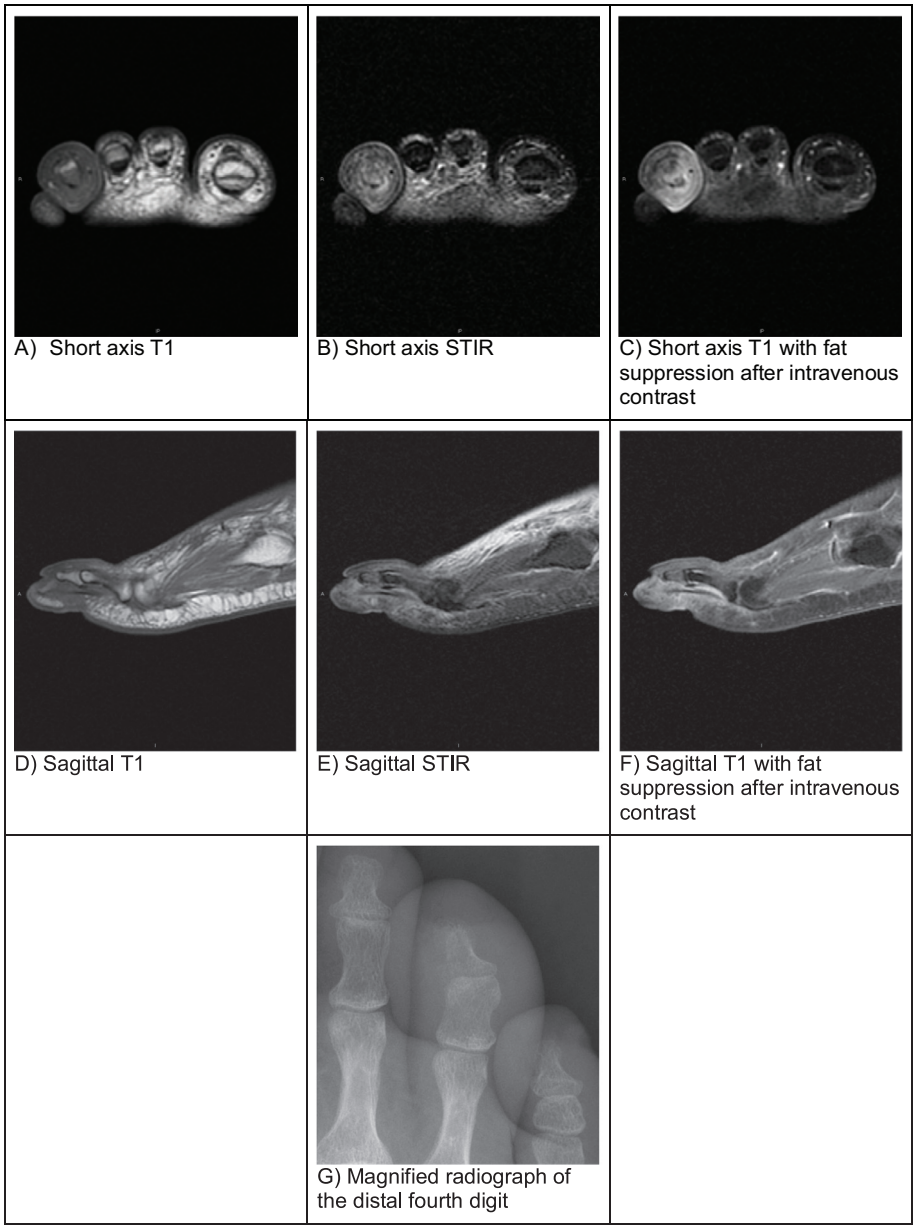


Fig. 4. A 38-year-old male without significant medical history presenting with uncomplicated cellulitis and osteomyelitis of the fourth digit. There is hypointense marrow signal on T1-weighted images of the fourth distal and middle phalanges (*A*,*D*). There is corresponding short-TI inversion recovery (STIR) imaging hyperintensity (*B*,*E*) and postcontrast enhancement (*C*,*F*). Soft tissue swelling and edema surround the fourth digit, tracking along the forefoot dorsum. Radiography better demonstrates cortical erosion of the distal phalanx (*G*). Imaging and clinical examination were negative for abscess or ulceration.

who had uncomplicated cellulitis (Table 5) (Fig. 4). Although that rate was higher than expected, OM remains uncommon in uncomplicated cellulitis, and routine MRI is therefore not recommended.

One of the strengths of this study is that, to our knowledge, it has the largest number of reviewed MRIs for evaluation of OM to date. Despite this, there are some limitations that should be considered when interpreting our results. Our data include patients from a single hospital in a large metropolitan area, and there may be differences in applicability compared with centers with different patient demographics. Furthermore, we evaluated the incidence of certain diagnoses documented through our EMR including cellulitis, ulceration, diabetes, PVD, and HLD/atherosclerosis because these have been shown to contribute to an increased risk of OM. This has some inherent limitations, including the occasional absence of clinical data which may introduce some degree of bias. Another possible limitation is unrecognized data entry or coding errors where some diagnoses may be over- or underreported at the time of admission, or at the time when MRI was performed. Finally, our study relies on the MRI diagnosis of OM as opposed to bone culture and histopathology. It would be helpful to conduct a study in which confirmatory bone biopsies were performed in conjunction with all MRI evaluations.

In conclusion, the perception that uncomplicated cellulitis often leads to underlying OM is not supported by this study. Furthermore, MRI should be reserved for those patients with considerable comorbidities and a high clinical index of suspicion for OM.

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