Foot metastasis: Current knowledge

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Abstract

Foot metastasis are rare and often overlooked due to non-specific symptoms. This often leads to misdiagnosis delaying the right diagnosis. Metastatic disease of the foot is rare. Foot pain and swelling may be the presenting symptom of an occult malignancy. If metastatic disease is not kept in the differential diagnosis of foot pain, diagnosis and treatment will be delayed. The purpose of this study was to analyze articles presenting cases of foot metastasis to provide a more accurate incidence of symptomatic foot acrometastasis as well as to review the clinical course and outcomes. Studies were searched on PubMed/Medline from the inception to February 2020. All studies included in the review presented foot metastasis either with or without a known primary tumor. Most of the articles were case reports, to which we added two case reports of foot acrometastasis produced by our Institute. Forty-three studies with a total of 53 patients were included in this review. The literature published mostly concerning case reports about old patients (average age: 63.2), in a late phase of their disease. Lung cancer appeared to be the most common primary tumor, followed by endometrial and breast cancer. In the 36% of the cases foot metastasis were found when the primary site was still unknown. Calcaneus and metatarsal bones were the most common bones involved. Surgical solution is rare, the chosen treatments are often of palliative care. Prognosis was often poor, death occurred within 2 years since the discovery of foot metastasis in about 50% of cases.

Introduction

Foot metastasis are a very rare occurrence in patients with an oncological history. Studies suggest that only the 0.007-0.3% of cancer patients develops acrometastasis2,3 metastasis to hands and feet and - among those, less than 50% involves feet. Therefore, these outbreaks are often underdiagnosed or misdiagnosed with a significative delay of the diagnosis, leading to several inappropriate treatments. This is the main reasons why foot metastasis have such a poor prognosis, in association with the fact that acrometastasis usually occur only after a widespread dissemination of the tumor.1 The tumor histotype is mainly lung cancer, followed by gastrointestinal-tract and genito-urinary tract tumors.3 Associated signs and symptoms are generally non-specific and can be identified with soft tissue swelling, functional impairment and intermittent pain.4 Metastasis diagnosis is often not considered at first because of the great account given to differential diagnoses, mostly associated to benign conditions such as gout, rheumatoid arthritis, ligamentous sprains, osteoarthritis or even Paget’s disease.5 Furthermore, estimates of foot acrometastasis are probably low owing to the common practice of excluding the distal extremities from metastatic skeletal surveys or whole-body computed tomography.6 There is a wide variety of treatments, from pharmacological therapy to External Beam Radiation Therapy (EBRT) and Surgery. These kinds of treatments have often a palliative aim, to grant a better quality of life.

Materials and Methods

A literature review using the PubMed/Medline database was performed (from the beginning to February 2020). The search strategies (using a combination of controlled vocabulary and text word terms) were: foot metastasis OR calcaneal metastasis OR calcaneum metastasis OR talus metastasis OR navicular metastasis foot OR cuboid metastasis OR cuneiform metastasis OR metatarsal metastasis OR phalax metastasis foot OR hindfoot metastasis OR forefoot metastasis OR midfoot metastasis OR soft tissue metastasis foot. Our research initially produced 221 articles, to which we added two case reports our Institute produced respectively in 20067 and in 2019.8 Studies in our review include both ones where foot acrometastasis were secondary to a known primary tumor, and ones where they were the first manifestation of a still unknown tumor, for which diagnosis was made afterwards. All duplicates, articles without full text and studies regarding primary tumors of the bone or soft tissue of the foot were excluded. Two review authors independently selected eligible articles. Disagreements at any stage were resolved by consensus or a third party adjudication. Descriptive statics was used to summarize the data. All the outcomes reported by each study were analyzed and when possible, data were pooled to generate frequency-weighted values to summarize outcomes.

Results

Following the PRISMA flow-chart (Figure 1),9 44 studies were finally included in the review (Table 1).7,8,10-51 In this review we gathered 46 different cases of patients with foot metastasis, including 25 females (54.4%) and 21 males (45.6) with an average age of 63.2 (+18.0) years old (Table 2). Thirty seven percent of patients presented acrometastasis as first manifestation of disease. The most common locations of primary tumors in patients with a positive history of neoplastic disease were the lung in 28.3% of cases, followed by endometrium (17.4%) and breast cancer (10.9%). Subsequently, we discuss the main features of the principle types of foot metastasis found in our review.7,8,10-51
| Author            | Year | N° of case | Sex | Age | Primary Site                        | Metastatic Site          | Diagnostic Imaging | Survival (months) |
|-------------------|------|------------|-----|-----|-------------------------------------|--------------------------|--------------------|-------------------|
| Cooper et al.     | 1994| 1          | F   | 59  | Occult - Endometrium               | Right calcaneus          | X-ray, BS          | 60                |
| Kemnitz et al.    | 1996| 1          | M   | 68  | Occult - Lung                       | Left 1° MT               | X-ray              | 5                 |
| Groves et al.     | 1998| 1          | F   | 58  | Breast                              | Left calcaneus           | X-ray, MR, CT, BS  |                  |
| Parikh et al.     | 1998| 1          | M   | 1   | Kidney                              | Right heel soft tissue   | CT, X-ray, BS      | 18                |
| Delgadillo et al. | 1998| 1          | F   | 42  | Occult - Lung                       | Right 3° MT              | X-ray, BS, MR      |                  |
| McGarry et al.    | 2000| 1          | M   | 45  | Occult - Lung                       | Right calcaneus          | X-ray, BS          |                  |
| Kaufmann et al.   | 2001| 1          | F   | 88  | Lung                                | Right calcaneus          | X-ray, BS          |                  |
| Oh et al.         | 2002| 1          | M   | 82  | Prostate                            | Right cuboid             | BS, X-ray, MR      |                  |
| Manolitas et al.  | 2002| 1          | F   | 76  | Occult - Endometrium               | Right calcaneus          | X-ray, BS          | 11                |
| Yadav et al.      | 2004| 1          | M   | 55  | Occult - Kidney                     |Right 2° MT               | X-ray              |                  |
| Osterhouse et al. | 2004| 1          | F   | 80  | Breast                              | Distal left and right tibia and fibula, left calcaneus | Bilateral X-ray |         |
| Kouvaris et al.   | 2005| 1          | F   | 59  | Breast                              | Left talus               | X-ray, MR, BS      | 18                |
| Amiot et al.      | 2006| 1          | F   | 86  | Endometrium                         | Left hallux distal phalanx | X-ray             |                  |
| Maccauro et al.   | 2006| 1          | F   | 64  | Occult - Kidney                     | Left talus               | X-ray, MRI, BS     |                  |
| Duarte et al.     | 2007| 1          | M   | 61  | Lung                                | Left 3° MT               | X-ray, BS, MR      |                  |
| Piazza et al.     | 2008| 1          | F   | 82  | Melanoma                            | Foot dorsum soft tissue |                   |                  |
| Allman et al.     | 2008| 1          | M   | 91  | Waldenstrom                         | Right hallux distal phalanx and left cuboid | X-ray, BS, MR, PET |                  |
| Agrawal et al.    | 2008| 1          | M   | 74  | Prostate                            | Left calcaneus and cuboid | BS, X-ray         |                  |
| Byti et al.       | 2009| 1          | F   | 37  | Breast                              | Right 2° MT              | X-ray, CT, BS      | 18                |
| Pichai et al.     | 2009| 1          | M   | 60  | Buccal Mucosa                       | Left talus               | CT, PET            | 24                |
| Ellington et al.  | 2009| 1          | M   | 48  | Colon                               | Left cuboid              | X-ray, MR, CT, BS  | 8                 |
|                  | 2009| 1          | F   | 70  | Rectum and lung                     | Right calcaneus          | X-ray, MR          |                  |
|                  | 2009| 1          | M   | 84  | Colon                               | Right foot soft tissue and 3° MT | X-ray, MRI, PET-CT | 13                |
| Dutta et al.      | 2011| 1          | M   | 53  | Esophagus                           | Right 1° MT              | X-ray, BS          |                  |
| Choufani et al.   | 2011| 1          | M   | 58  | Occult - Kidney                     | Right foot medial and middle cuneiform | X-ray, CT       |                  |
| Iselin et al.     | 2011| 1          | M   | 62  | Occult - Lung                       | Narivocal bone           | X-ray, CT, MR, BS  | 12                |
| Pieters et al.    | 2011| 1          | F   | 76  | Endometrium                         | Left sinus tarsi and calcaneus | X-ray, MR        | 36                |
| Wijayaratna et al.| 2013| 1          | F   | 88  | Occult - Colon-rectum               | Left 1° MT               | MR, PET            |                  |
| Ryder et al.      | 2013| 1          | F   | 82  | Occult - Urothelial of the ureter   | Left calcaneus           | X-ray, MR, BS, CT  | 21                |
| Samuelani et al.  | 2013| 1          | M   | 52  | Pharynx                             | Right foot soft tissue   | CT, PET-CT, US, X-ray | 9                 |
| Dai et al.        | 2014| 1          | F   | 58  | Occult - Lung                       | Left calcaneus           | X-ray, CT, MR, BS  | 6                 |
| Rice et al.       | 2014| 1          | F   | 86  | Endometrium                         | Left calcaneus           | X-ray, MR, PET-CT  | 1                 |
| Kaynak et al.     | 2014| 1          | M   | 55  | Lung                                | Left talus               | MRI, BS            | 4                  |
| Rice et al.       | 2015| 1          | F   | 82  | Lung                                | Right talus              | X-ray, BS          | 1                  |
| Reyes et al.      | 2015| 1          | M   | 64  | Prostate                            | Left navicular           | BS, CT, MRI, WBC scan, X-ray |                  |
| Long et al.       | 2015| 1          | F   | 62  | Occult - Endometrium               | Left 5° MT               | X-ray, CT, MR      |                  |
| Kumar et al.      | 2015| 1          | F   | 54  | Urothelial of the bladder           | Left 1°, 2° and 3° MT    | MR, X-ray, PET     |                  |
| Jaffe et al.      | 2016| 1          | F   | 56  | Breast                              | Left talus and soft tissue | X-ray, MR, BS     |                  |
| Singh et al.      | 2016| 1          | F   | 63  | Occult - Lung                       | Left calcaneus           | MR, BS, CT, FDG-PET |                  |
| Li et al.         | 2016| 1          | M   | 61  | Occult - Lung                       | Left cuneiform           | BS, SPEC-CT       |                  |
| Gan et al.        | 2017| 1          | M   | 66  | Occult - Lung                       | Left talus               | X-ray, CT, MRI     |                  |
| Tonogai et al.    | 2018| 1          | M   | 59  | Kidney                              | Left calcaneus           | X-ray, CT, MRI     |                  |
| Martin et al.     | 2018| 1          | M   | 71  | Lung                                | Right talus              |                   |                  |
| Nasr et al.       | 2018| 1          | F   | 14  | Chest wall Ewing’s sarcoma          | Left talus               | PET, CT, BS, MR    |                  |
| Madabhani et al.  | 2019| 1          | F   | 66  | Occult - Endometrium               | Multiple right tarsal bones | X-ray, BS        |                  |
| Perisano et al.   | 2019| 1          | F   | 50  | Endometrium                         | Left cuboid, IV-V MT     | US, X-ray, PET-CT  | 8                 |

MT Metastasis; BS Bone Scan; MR Magnetic Resonance; US Ultrasonography; PET Positron Emission Tomography.
Lung Cancer
Among the foot metastasis taken into account, the largest number of them takes origin from lung cancer. This reflects both the prevalence of lung carcinoma and its predilection for the skeleton in metastatic spread. These kinds of lesion in more than half of cases represent the first occurrence, even before the diagnosis of the primary tumor. Commonly, the localization is at the hindfoot (talus and calcaneus), and rarely metastasis involve 2 or more bones of the foot. The chances of survival after the diagnosis of foot metastasis are very low, indeed the majority of the patients dies in few months.11,15,29,32,37,39,40

Gynaecological and Breast Cancer
Gynaecological cancers are well described, with 8 cases referring about foot metastasis. Within “women’s cancers” - breast and uterus - endometrial carcinoma is the first primary tumor related to this kind of metastasis in this group, strictly followed by breast cancer. Foot metastasis in gynaecological cancers often occur on the calcaneus and are characterized by lesions which are mostly lytic. Carcinoma of the uterus and Breast cancer differ in timing of diagnosis of the primary lesion: foot metastasis are often the first occurrence to be noticed in patients affected by endometrial cancer. Breast cancer, instead, is already diagnosed at the time of foot metastasis discovery.12,26,31,27,44

Genito-urinary Cancer
Genito-urinary cancer usually involves bones in metastatic dissemination. Kidney and prostate tumors are the most related to foot metastasis, but the kind of lesions they determine are not the same: renal cancer, is usually linked to the occurrence of lytic lesions, as it happens to most of other tumors. Bone metastasis from prostate cancer, instead, are osteoblastic, sclerotic lesions. Multiple foot bone lesions are not rare. Moreover, two articles described cases of tumors of urothelial origin (one of the urether and one of the bladder

Table 3. Localization of foot acrometastasis.

|                       | Total |
|-----------------------|-------|
| Hindfoot              |       |
| Calcaneus             | 14    |
| Talus                 | 9     |
| Midfoot               |       |
| Cuboid                | 5     |
| Navicular             | 2     |
| Cuneiforms            | 2     |
| Forefoot              |       |
| Metatarsal bone       | 11    |
| Phalanx               | 2     |
| Soft tissue           |       |
| Total                 | 5     |

Table 2. Patient demographics, type of tumor, biopsy and treatment.

| Total Case | 45 |
|------------|----|
| Sex        |    |
| F          | 25 (53.3%) |
| M          | 21 (46.7%) |
| Average age| 63.2 ± 18.0 |
| Type of tumor |      |
| Lung       | 13/46 (28.3%) |
| Endometrium| 8/46 (17.4%) |
| Breast     | 5/46 (10.9%) |
| Kidney     | 5/46 (10.9%) |
| Colon-rectum | 4/46 (8.7%) |
| Prostate   | 3/46 (6.5%) |
| Urinary tract | 2/46 (4.3%) |
| Single case (Esophagus, Melanoma, W. Macroglubilinemia, Pharynx, Buccal Mucosa, Chest wall Ewing’s sarcoma) | 6/46 |
| Primary Occult |      |
| Yes | 17/46 (37%) |
| No  | 29/46 (63%) |
| Biopsy |          |
| Total | 41/45 (91.1%) |
| Open biopsy | 17/41 (41.5%) |
| FNA | 15/41 (36.6%) |
| Aspiration of sinovial fluid | 1/41 (2.4%) |
| Not specified type of biopsy | 8/41 (19.5%) |
| Treatment |          |
| Refused | 1 |
| Radiotherapy (alone or with surgery) | 27 |
| Surgery | 17 |
| Not specified | 4 |
| Survival (months) |        |
| Average | 15.2 ± 13.6 |
| Range   | 1-60 |

Figure 1. PRISMA flow-chart.

Records identified through database searching (n = 221) Additional records identified through other sources (n = 2)
Records after duplicates removed (n = 140)
Records screened (n = 78)
Full-text articles assessed for eligibility (n = 46)
Studies included in qualitative synthesis (n = 44)
Records excluded, with reasons (n = 24)
Full-text articles excluded, with reasons (n = 2)
Gastrointestinal-Tract Cancer

Gastrointestinal-tract cancer is also related to foot metastasis, but reported cases are much less than the aforementioned ones. Colo-rectal cancer is the most common one. Secondary foot lesions occurring in these cases are usually lytic lesions diagnosed during primary tumor follow-up. Thus, foot metastasis are linked to a worst prognosis. Most of the patients died within a year since the foot metastasis diagnosis. Our review also included a single case of metastatic metastatic bone lesion originating from esophageal cancer.

Others

Single cases of foot metastasis are reported in patients with Waldenström Macroglobulinemia, Ewing’s Sarcoma, Melanoma, Pharynx and Buccal Mucosa. In each of them, the primary tumor was already diagnosed at the time foot metastasis was discovered.

Discussion

Symptoms

The onset of the symptoms in foot metastasis is generally non-specific and can be identified with soft tissue swelling, erythema, functional impairment and intermittent pain. Usually this leads to a misdiagnosis, the most common foot problems come up in differential diagnosis such as heel spur, plantar fascitis, Haglund’s syndrome, etc. Therefore, before the correct diagnosis was found, patients went under different and unnecessary treatments, like simple analgesia or orthotics in patients. Diagnosis and Investigation

The diagnostic process was more or less the same for each patient, starting from an X-ray examination in 80% of cases. Among the 46 cases we have taken into account, only in 9 cases patients did not undergo X-Ray examination. MRI and CT, together with bone scan, are the most commonly examinations used by physician in these cases, both looking for the primary tumor (in 17 cases foot metastasis were diagnosed before finding the primary tumor) and analyzing the foot lesion itself. During a deeper investigation 19 patients showed other metastasis in different body districts (bone and/or parenchymatous). Forty-one of the 45 patients (91.1%) who accepted the treatment underwent a biopsy for histological confirmation and definitive diagnosis. Among these, 17 patients underwent an open biopsy.

Localization

The hindfoot was a common metastatic site (Calcaneus and Talus), with 23 occurrences (Table 3), followed by the forefoot and midfoot (15 and 9 localizations, respectively). Among single bones, 14 patients had findings at the Calcaneus, 9 at the Talus and 5 at the Cuboid. Eleven patients had metastasis at metatarsal bones.

Treatment and Prognosis

Treatment options are numerous and various, from simple palliative care (5 patients) to surgical intervention. Only one patient refused every kind of therapy.

The treatment was rarely surgical, most of the patients were not eligible for a surgical approach, only 17 of 44 patients were taken to the operating room. No surgical choices were clearly prominent, 6 patients underwent simple curettage, 6 others had an excision of the metastatic lesion, and only 5 of them had a more radical surgery (disarticulation/amputation or wide resection). Despite surgical intervention, the prognosis remained poor.

Radiotherapy on the metastasis site, whether alone or pre/post-surgery, was delivered to 27 out of 44 patients, often with palliative purposes. Systemic therapies, such as chemotherapy, hormonal therapy and biological drugs, were also given to reach a better prognosis for both primary and secondary lesions. Five patients only had palliative care. Most of them had a poor prognosis.

We found prognosis information for 20 out of 46 cases. Eighteen of them died within 2 years, more than half of them within 1 year (10 patients).

Conclusions

Metastatic tumors of the foot present special challenges in diagnosis and management, and are usually found in widespread cancer disease. Interestingly, in our series a wide variety of tumors is able to metastasize to the foot and highlighting that most primary cancers should be considered as having the potential to metastasize to the foot. In a meaningful number of cases, foot acrometastasis are the first sign of disease. Thirty seven percent of cases from our review presented acrometastasis as the first sign of malignancy. This is an interesting finding since, in past literature, acrometastasis as first presentation of occult malignancies was estimated to be around 10%. Foot metastasis have likely become more frequent throughout the years, both because neoplastic patients tend to live longer and clinicians probably are more aware of the malignant potential of foot lesions. The finding of foot metastasis is indicative of an already advanced disease and a poor prognosis. Average survival in our review was 15.2 months (+ 13.63) similarly with the literature. Patients often presented with a history of swelling, pain, functional impairment, skin changes, ulcers, lesions and sometimes drainage. This underlines the importance of a thorough history taking and physical examination in patients with these symptoms and especially in those with a known history of cancer. These lesions are often misdiagnosed as other more common pathologies (i.e. infections, gout, etc.) and do not improve with standard treatment for the aforementioned conditions. It has been reported that the diagnosis of an osseous metastasis of the foot is often delayed for between 1 and 24 months. However, plain radiographs, bone scan, MRI, CT, and biopsy usually reveal the underlying diagnosis. Since foot metastasis are very rarely observed, there is no standard protocol for treatment; treatment should be tailored to the single patient according to individual needs and life expectancy. Therapeutic management should be assigned to a multidisciplinary team made by oncologists, orthopedic surgeons, radiotherapists and, if necessary, vascular and plastic surgeons. Because of the poor prognosis, treatment is aimed at palliation: goals should be to control local symptoms and preserve function.

Treatment, which depends on the patient’s prognosis, may consist of cast immobilization, bracing, narcotics, anti-inflammatories, surgical amputation, local resection with or without augment, systemic chemotherapy, and local radiation.

Definitive surgical intervention can be planned if the patient is a surgical candidate. In addition, patients may elect for non-operative treatment based on their projected lifespan. However, reconstruction or amputation may improve a patient’s remaining quality of life. The decision between reconstruction and amputation is complex, requiring a discussion with the patient on a case-by-case basis. Reconstructive efforts should be aimed not only to preserve the limb but also to avoid creating local or distant metastasis.

When facing a patient older than 40 years old presenting with a foot lesion, the

[page 72] [Orthopedics Reviews 2020; 12(s1):8671]
chances of it being malignant should always be kept in mind to avoid delaying diagnosis and treatment, which could improve pain control and quality of life and increase the chances of preserving the involved limb. Foot metastasis must always be included in the differential diagnosis when the clinical picture raises suspicion.

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