Research Article

Clinicopathological and prognostic characteristics of acral metastases in patients with malignant disease: A retrospective study

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ABSTRACT

Objective: This study aimed to investigate the clinical, pathological, and prognostic characteristics of acral metastases in patients with malignant disease and to determine the impact of different types of acral metastasis treatment on patient survival.

Methods: In this retrospective study, 64 acral metastatic lesions in 46 patients (17 women, 29 men; mean age, 61.5 years; age range, 35-82 years) who were evaluated by the Bone and Soft Tissue Tumors Council of our institute from 2015 to 2019 were included. The patients’ primary tumor site, tumor type, localization of acral metastases, main symptom, duration from the diagnosis of the primary tumor to the diagnosis of acral metastasis, duration from the diagnosis of acral metastasis to death, and survival data were analyzed. The diagnosis of acral metastasis was confirmed by histopathological evaluation in 38 patients and clinical and radiological assessment of the lesions in 8 patients. The treatment type for each acral metastasis was individualized by the institutional Bone and Soft Tissue Tumors Council and categorized into 3 groups: excisional surgery (amputations and resections), palliative surgery (prophylactic fixation, intralesional curettage, and bone cement augmentation), and non-surgical treatment (chemotherapy, radiotherapy, and hormone therapy).

Results: A total of 16 acral metastases (25%) were identified in the upper extremity and 48 (75%) in the lower extremity. The most common primary tumor site was the lungs (32.6%), and the most common tumor type was adenocarcinoma (43.2%). The most frequent symptom and the primary reason for admission was pain (58.7%). The mean duration between the diagnosis of primary tumor and the diagnosis of acral metastasis was 19.1 (range, 0-124) months. No significant correlation was determined between the primary tumor types and duration from the diagnosis of primary tumor to the diagnosis of acral metastasis (p=0.278). Acral metastases were treated by excisional surgery in 15 (32.6%) patients, palliative surgery combined with non-surgical treatment in 10 (21.7%) patients, and only non-surgical treatment modalities in 21 (45.7%) patients. No significant correlation existed between the treatment types and patient survival (p=0.058). At the final follow-up, 30 (62.5%) patients were dead owing to the disease. The mean overall survival of the entire study group was 24.9 (range, 3-55) months. The mean duration between the diagnosis of acral metastasis and death was 7.6 (range, 3-24) months in patients who were dead owing to the disease (p=0.012).

Conclusion: When the diagnosis of acral metastasis is established, it should be borne in mind that the most common primary tumor site and type are most likely the lungs and adenocarcinoma, respectively. The treatment type for acral metastasis may have no significant impact on patient survival, but the extensiveness of the disease may be a critical factor for survival.

Level of Evidence: Level IV, Prognostic study

Introduction

Bone is the third leading site for metastases, after the lung and liver, and approximately 15% of all carcinomas clinically manifest bone metastases (1). The most frequent part of the skeleton for metastatic bone disease is the axial skeleton, especially the thoracic and lumbar spine, followed by the bony pelvis (1). Bone metastases generally affect bones that are rich in red marrow (2). In the limbs, the incidence decreases from proximal to distal, and metastases that are distal to the knee and elbow are distinctly rare (1).

There is a global confusion, misunderstanding, and misuse of the term “acrometastasis” in the literature. Some authors use this term to describe the metastatic lesions located in the hands and feet, whereas others use it for metastases that are located distal to the elbow and knee (2-7). In a recent study, metastases distal to the elbow and knee, such as metastases in the hands and feet, have been highlighted as signs of poor prognosis and were shown to occur earlier in the course of the disease (8). Therefore, the term “acral metastases” is used to describe the metastases distal to the elbow and knee till the fingertips (covering both the metastases distal to the elbow and knee and metastaes in the hands and feet) in this study (9, 10).

The metastatic lesions located distal to the elbow and knee represent approximately 0.1%-7% of all bone metastases (5, 9, 10). Acral metastases are frequently found in patients with widespread disseminated disease; however, in some patients, acral metastases may be the first sign of malignancy (5). It has been shown that in 10% of the patients, acral metastases may be the first presentation of an occult silent malignant disease (6, 11).

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Patients with acral metastases usually present with progressive pain, swelling, non-healing wounds, and ulcerations (Figure 1). Because recognition of these lesions is not very easy, especially in patients with an undiagnosed malignant disease, they are often misdiagnosed as infectious and inflammatory lesions, such as diabetic foot, chronic venous ulcerations, paronychia, gout, osteomyelitis, tuberculous dactylitis, and often osteoarthritis (2, 5, 6).

Acral metastases are considered as dissemination of the malignant cells through the entire blood flow and are believed to be a manifestation of poor prognosis (5, 6). Increase in the incidence of acral metastases is observed in the literature parallel to the increased survival of patients owing to the improvements in oncologic treatment (2). Small-cell lung tumors are reported as the most frequent cause of acral metastases; however, other cancer types and malignant diseases are also reported as primary lesions for acral metastasis in the literature (3, 5, 6, 12).

The objective of this study was to determine which organ tumors and which tumor types most commonly cause acral metastasis, to evaluate the treatment options for survival of patients, and to raise awareness among clinicians about non-traumatic distal extremity lesions, particularly in the elderly with both unknown and diagnosed malignant disease.

Materials and Methods

This study was approved by the local ethics committee for scientific research of the Trakya University, School of Medicine with the approval number of TÜTF-BAEK 2019/453. The data of all the patients with extremity metastases distal to the knee and elbow, who were evaluated by the Bone and Soft Tissue Tumors Council of Trakya University Health Center for Medical Research and Practice Hospital between January 2015 and November 2019, were analyzed retrospectively.

The clinical, radiological, and histopathological confirmation of the acral metastatic lesions were evaluated and noted.

The treatment option for each patient was individualized by the institutional Bone and Soft Tissue Tumors Council according to the patients’ general performance, life expectancy, metastases to major internal organs, localization of primary tumor, localization of the acral metastasis, and operability of the lesion. The treatment modalities were grouped as excisional surgery (amputations and resections), palliative surgery (prophylactic fixation or intralesional curettage and bone cement augmentation), and non-surgical treatment (chemotherapy, radiotherapy, and hormone therapy).

Epidemiological data regarding age, sex, primary tumor site, type of primary tumor, main symptom, localization of acral metastasis, presence of other skeletal and extraskeletal metastases, time period between diagnosing primary tumor site and acral metastasis, treatment, and survival of the patients were collected from the medical archives of the institution. All the collected data were analyzed statistically to determine which tumor types and localizations most commonly cause acral metastases and to investigate the possible association between the treatment options and survival.

Statistical analysis

All the statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 22.0 (IBM SPSS Corp.; Armonk, NY, USA). Mean, standard deviation, and median values were calculated for numerical variables. Differences in quantitative variables between the groups were measured using the Kruskal-Wallis test, and quantitative differences between the groups were evaluated using the Fisher’s exact test. Survival analysis between the groups was studied using the Kaplan-Meier survival analysis. In all the analyses, p<0.05 was set as statistically significant with a 95% confidence interval.

Results

There were 46 patients with 64 acral metastatic lesions. There were 17 women (36.9%) and 29 men (63.1%). The mean age of patients was 61.5 (range, 35-82) years. A total of 16 (25%) acral metastases were found in the upper extremities and 48 (75%) in the lower extremities (Table 1).

HIGHLIGHTS

- Acrometastases are frequently found in patients with widespread disseminated disease, but in some cases, acrometastases can be the first sign of a malignant disease.
- Recognition of these lesions is not very easy, especially in cases with an undiagnosed malignancy; they are often misdiagnosed as infectious and inflammatory lesions.
- Acrometastases have a negative influence on patients with oncologic disease by limiting their physical activity, discouraging and causing failure in sustaining against malignancy.
- Clinicians should be aware of non-traumatic distal extremity lesions, especially in elderly people with both unknown and diagnosed malignant disease.
Pain was the most common symptom and the primary reason for admission in patients with acral metastases in our study. When the reasons for admission were analyzed, it was found that 27 (56.7%) patients were admitted because of intolerable pain, 6 (13%) patients because of pathological fractures, and 4 (8.7%) patients because of palpable masses. The remaining patients in this study were referred from the oncology unit with asymptomatic acral lesions detected during routine scanning.

Table 1. Distribution of acrometastatic lesions’ localization in the upper and lower extremity

| Localization | Upper extremity (n=16), n (%) | Lower extremity (n=48), n (%) |
|--------------|-----------------------------|-------------------------------|
| Radius       | 8 (50)                      | 33 (68.75)                    |
| Ulna         | 3 (18.75)                   | 7 (14.5)                      |
| Carpal       | 0                           | 6 (12.5)                      |
| Metacarpal   | 2 (12.5)                    | 0                             |
| Phalanx      | 3 (18.75)                   | 2 (4.25)                      |

Table 2. Localization and tumor types of the patients’ primary tumors

| Primary tumor type | Localization                        | Number of patients (n=46), n (%) |
|--------------------|-------------------------------------|---------------------------------|
| Adenocarcinoma     | Pulmonary                            | 8 (17.39)                       |
|                    | Invasive ductal carcinoma           | 3 (6.52)                        |
|                    | Prostate                            | 2 (4.34)                        |
|                    | Endometrium                         | 2 (4.34)                        |
|                    | Renal cell carcinoma                | 2 (4.34)                        |
|                    | Colon                               | 2 (4.34)                        |
|                    | Stomach                             | 1 (2.17)                        |
| Hematological      | Lymphoma                            | 8 (17.39)                       |
| malignancy         | Multiple myeloma                    | 4 (8.69)                        |
| Sarcomatoid        | Sarcomatoid renal cell carcinoma    | 2 (4.34)                        |
|                    | Histiocytic sarcoma (inner ear)     | 1 (2.17)                        |
|                    | Angiosarcoma (gluteal)              | 1 (2.17)                        |
| Squamous-cell      | Pulmonary                            | 7 (15.21)                       |
| carcinoma           | Larynx                              | 3 (6.52)                        |

Adenocarcinomas were the most frequent (43.5%) histopathological type of primary tumor that caused acral metastases in this study, followed by hematological malignancies (26.1%), squamous-cell carcinomas (21.7 %), and sarcomatoid tumors (8.7%) (Table 2). The primary tumor sites were the lungs (32.6%), reticuloendothelial system (26%), kidneys (8.7%), breast (6.5%), larynx (6.5%), colon (4.4%), prostate (4.4%), uterus (4.4%), inner ear (2.2%), stomach (2.2%), and skeletal muscle (2.2%) (Table 2).

The mean duration between the primary tumor diagnosis and the diagnosis of acral metastasis was 19.1 (range, 0-124) months. The mean duration between the primary tumor diagnosis and the diagnosis of acral metastasis was 16.7 (range, 0-124) months for the adenocarcinoma group, 40.2 (range, 0-120) months for the hematological malignancies, 16 (range, 0-63) months for the sarcomatoid tumors, and 8.5 (range, 0-29) months for the squamous-cell carcinoma group. There was statistically no significant correlation between the tumor types and duration between the diagnosis of primary tumor and the diagnosis of acral metastasis (p=0.278).

It was found that acral metastases were the first sign of malignant disease in 20 (43.5%) patients in the study (Figure 2). Acrall metastases presented as a part of disseminated disease in 28 (60.8%) patients, whereas solitary acral metastases were found in 18 (39.1%) patients. In patients with disseminated disease, acral metastases were accompanied by pulmonary metastases (11 patients), lymph node metast-
spread is the keystone mechanism of acral metastasis. An increase of reported that 50% of the patients presenting with an acral metastasis through the left atrium and ventricle (2, 7). Furthermore, it has been tent with the literature (3, 5, 6, 12). Pulmonary tumors have direct ac...tases (forearm or lower leg), and acrometastases (hands and feet) as body trunk metastases, rhizometastases (arm or thigh), mesometastases (forearm or lower leg), and acrometastases (hands and feet) and investigated their effects on the prognosis and outcome (8). The authors stated that mesometastases appear earlier than acrometastases in the course of the disease, and both represent disease dissemi-
nation and poor prognosis. The authors recommend palliative rather than invasive management in patients with acrometastases and mesometastases. Treatment of acral metastases is still debated, and there is no treatment protocol because of the rarity of the entity (6). Treatment of acral metastatic lesions must be planned on the basis of whether the metastasis is solitary or multiple. A complete staging must be performed in every patient, even in those with disseminated disease with multiple metastases. A detailed investigation of the thoracic and abdominal areas using computed tomography and total-body bone scan to evaluate the visceral organs and to detect the multiplicity and extent of bone metastases is the traditional option for staging. Positron emission tomography scan is used by our Bone and Soft Tissue Tumors Council instead of total-body bone scan because of its increased sensitivity (16). In our study, aggressive treatment with wide resection (often amputations for acral metastases of the hand and foot) in case of a solitary acral metastasis was performed. The treatment options vary in patients with disseminated disease; location and the extent of the lesion, expected survival, overall performance of the patient, and primary tumor type are the variables affecting the decision on the treatment options. Treatment options should be individualized and performed on a case-by-case basis allowing the treatment of the primary tumor. Goals of the treatment should be focused on symptomatic relief and functional restoration although usually short-term palliation is targeted (6, 13). Healey et al. reported that amputation and curettage were the surgical options for acral metastasis (3). Machado et al. reported en bloc resection and reconstruction with autologous or heterologous structural grafting in 50% of their patients, whereas the remaining patients were treated with cryosurgery, cement filling, amputation, and prophylactic nailing (5). Leeson et al. reported that 8 of 57 patients received surgical treatment in their study (4). Nearly one-third of the patients were treated with excisional surgery in our study, whereas 21.7% of the patients received supportive surgery combined with non-surgical treatment, and 45.7% of the patients had only non-surgical treatment.

With modern drugs, radiosurgery, and improvements in surgical capabilities, survival of patients with oncologic diseases is increasing (6). Although acral metastases are rarely seen entities, their prevalence is increasing owing to the increase in the life-span of the patient population with oncologic diseases. The most common primary tumor that causes acral metastasis is the lung tumor; however, hematologic malignancies and other sources of malignant diseases should also be kept in mind. The treatment depends on various factors but by any measure, acral metastasis is a sign of poor prognosis (2).

Acral metastases are most commonly seen in pre-terminal patients with widespread disease and are considered to be an indicator of poor outcome. Various data on the survival rate of patients with acral metastasis are available in the literature, and some authors suggest that these results have not changed over the last 25 years (2, 3, 5, 7, 11, 12). However, renal cell carcinoma metastases appear as an exception, and it has been shown that aggressive surgical resection prolongs the survival beyond 12 months, especially in patients with a long interval between nephrectomy and acral metastasis (2, 6, 13).

The best overall survival regarding the histological type of primary tumor was in patients with adenocarcinoma (9.7 months) in this study. However, we believe that this fact is not applicable for all the patients with adenocarcinoma, such as a pulmonary adenocarcinoma and prostate adenocarcinoma. There were 8 patients with pulmonary adenocarcinoma in our study; in 5 of them, acral metastases were the first sign of malignancy, and only 1 of them is still alive.

The reason for this overall survival rate can be explained with the presence of other adenocarcinomas, such as bladder, prostate, and breast adenocarcinomas, which are less aggressive than the other tumor cases in our study group (Table 2).

This study had several limitations. The first limitation is about the treatment options of 3 patients. In 3 patients, amputations were performed without a prior biopsy. These 3 patients were in poor condition with lowered Karnofsky performance scale values. In addition, one of them was bed-ridden for 2 months because of the acral metastasis in his tarsal bones with severe sacral decubitus ulceration. Heterogeneity of the patient group in terms of extraskeletal metastases and primary tumor locations is another limitation of the study. In fact, patients with primary pulmonary tumors should be treated separately for acral metastases as the pulmonary tumor metastases bypass the pulmonary filter and pass directly into the systemic circulation, making metastases easier for the acral regions of the body.

This study emphasizes the importance of acral metastasis by reviewing the epidemiological evidence, examining which primary tumor types and locations most frequently cause acral metastases, and investigating the potential associations between treatment options and survival. A high level of concern and suspicion is required in case of a distal extremity complained from a patient with previously diagnosed cancer or in patients with constitutional symptoms, such as weight loss, anemia of uncertain cause, fatigue, loss of appetite, malaise, and dyspnea of an undiagnosed malignant disease.

In conclusion, acral metastases are serious manifestations of malignant disease and are a sign of dissemination of disease through the hematomatologic route. These lesions should be diagnosed and treated appropriately to promote the progression and sustainment of the oncologic treatment and to support the patient.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethical Committee of Trakya University, School of Medicine.

Informed Consent: Written informed consent was obtained from the patients.

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References
1. Campanacci M. Bone and Soft Tissue Tumors. Padova: Piccin Nuova Libraria and Wien. New York: Springer; 1999.
2. Stoneo D, Tourl I, Ziruna A, Perissino C, De Santis V, Maccagno G. Acrometastasis: A literature review. Eur Rev Med Pharmacol Sci 2015; 19: 2906-15.
3. Healey JH, Turnbull A, Miedema B, Lane J. Acrometastases. A study of twenty-nine patients with osseous involvement of the hands and feet. J Bone Joint Surg Am 1986; 68: 743-46. [Crossref]
4. Leeson MC, Makley JT, Carter JR. Metastatic skeletal disease distal to the elbow and knee. Clin Orthop Relat Res 1986; 206: 94-9. [Crossref]
5. Machado V, San-Julian M. Prognosis and treatment of acrometastases: Observational study of 35 cases treated in a single institution. Rev Esp Cir Ortop Traumatol 2019; 63: 49-55. [Crossref]
6. Mavrogenis AF, Mimidis G, Kokalis ZT, et al. Acrometastases. Eur J Orthop Surg Traumatol 2014; 24: 279-83. [Crossref]
7. Muñoz-Mahamud E, Combalia A, Carreño A, Arandes JM. Five cases of acrometastasis to the hand from a carcinoma and review of the literature. Hand Surg Rehabil 2017; 36: 124-6. [Crossref]
8. Tani S, Morizuki Y, Usuda K, et al. Bone metastasis of limb segments: Is it metastasis another poor prognostic factor of cancer patients? Jpn J Clin Oncol 2020; 50: 668-92. [Crossref]
9. Yochum TR, Rowe LJ. Tumors and Tumor-Like Processes. In: Yochum TR, Rowe LJ, editors. Essentials of Skeletal Radiology. Philadelphia, UNITED STATES: Wolters Kluwer Health; 2004. p. 1137-372.

10. Lipton JF, Vigorita VJ. Metastatic Bone Disease. In: Vigorita VJ, editor. Orthopaedic Pathology. Philadelphia, UNITED STATES: Wolters Kluwer; 2015. p. 1033-78.

11. Khokhar N, Lee JD. Phalangeal metastasis: First clinical sign of bronchogenic carcinoma. South Med J 1963; 76: 927. [Crossref]

12. Morris G, Evans S, Stevenson J, et al. Bone metastases of the hand. Ann R Coll Surg Engl 2017; 99: 563-7. [Crossref]

13. Spiteri V, Bilba A, Ashwood N, Cobb J. Managing acrometastases treatment strategy with a case illustration. Ann R Coll Surg Engl 2008; 90: 8-13. [Crossref]

14. Ellington JK, Kneisl JS. Acrometastasis to the foot: Three case reports with primary colon cancer. Foot Ankle Spec 2009; 2: 140-5. [Crossref]

15. Barnes M, Tiwana MS, Kiraly A, Hutchinson M, Olson RA. Incidence of distal bone metastases in patients treated for palliative radiotherapy and associations with primary tumour types. J Bone Oncol 2015; 4: 107-9. [Crossref]

16. Ohta M, Tokuda Y, Suzuki Y, et al. Whole body PET for the evaluation of bony metastases in patients with breast cancer: comparison with 99Tcm-MDP bone scintigraphy. Nucl Med Commun 2001; 22: 875-9. [Crossref]