

Skin toxicity can present with a wide spectrum of manifestations: pruritus, urticaria, a maculopapular or, more rarely, petechial rash, photosensitivity, exudative erythema multiforme major, toxic epidermal necrolysis, and vasculitis.^{1,6} Exposure to diltiazem is a rare but well-documented cause of AGEP.¹⁻¹¹ The Table summarizes the clinical features and course of the 13 cases reported up to now in the literature in English and Spanish, including the present case (search in PubMed using the key words: “diltiazem” or “calcium-channel blocker” and “pustulosis” or “AGEP”). The review of these cases shows a marked female predominance (male to female ratio, 2 to 11). The delay in the onset of symptoms varies between 24 hours⁹ and 3 weeks⁷ after starting treatment with diltiazem (mean [SD], 11.4 [5.5] days). After withdrawal of treatment, complete resolution of the rash occurs in 7.3 (2.4) days. Those cases in which the accidental rechallenge was documented provide the most conclusive evidence in favor of the implication of diltiazem as a trigger of the condition.^{8,9} The use of patch tests constitutes a valid option for confirming this association, as positive results have been found in all cases in which those tests were performed.^{1,2,7,9} In conclusion, the calcium channel blockers and, in particular, diltiazem, must be considered to be potential triggers of AGEP. Positive skin patch testing will confirm the diagnosis in cases of atypical clinical presentation.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Chronic Painless Dactylitis as the Initial Finding in Disseminated Lung Adenocarcinoma

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To the Editor:

Cutaneous metastases secondary to primary visceral tumor are uncommon events, occurring in 0.7% to 9% of cases.^{1,2} They usually appear in patients previously diagnosed with a primary tumor. We present the case of

a patient who developed chronic painless dactylitis that was histologically compatible with a previously unknown underlying metastatic lung adenocarcinoma.

The patient was a 56-year-old woman, a nonsmoker with hypertension, who was admitted for evaluation

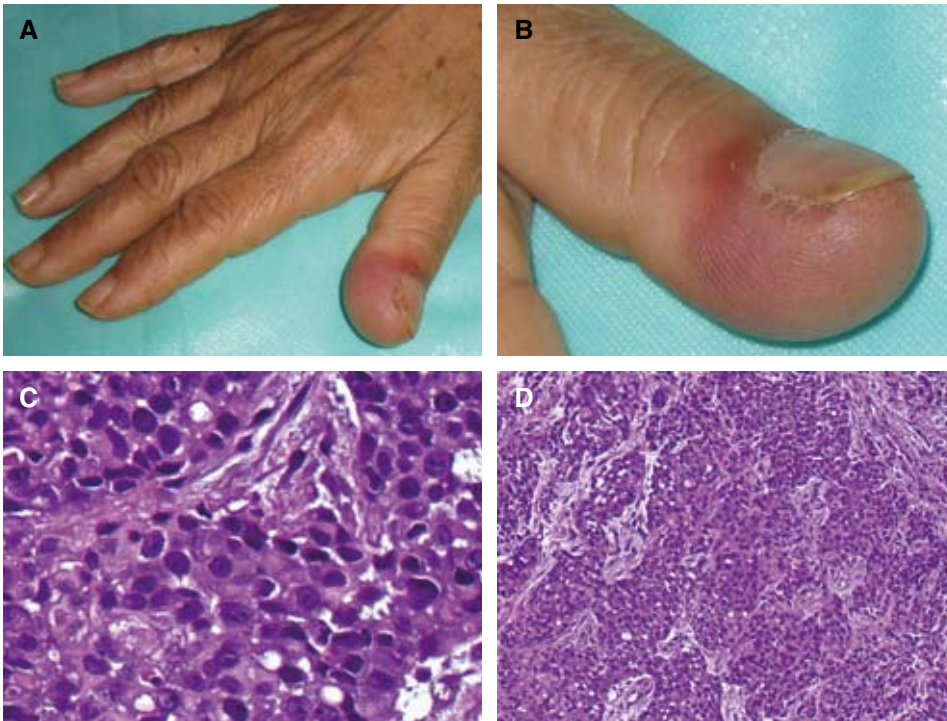


Figure 1. A and B. Thickening and induration of a finger on the right hand with violaceous coloring. C. Infiltration of the deep dermis and subcutaneous cell tissue by atypical cells distributed in a trabecular pattern. (Hematoxylin-eosin, $\times 40$) D. The trabeculae are separated by bands of fibrous tissue. (Hematoxylin-eosin, $\times 100$).

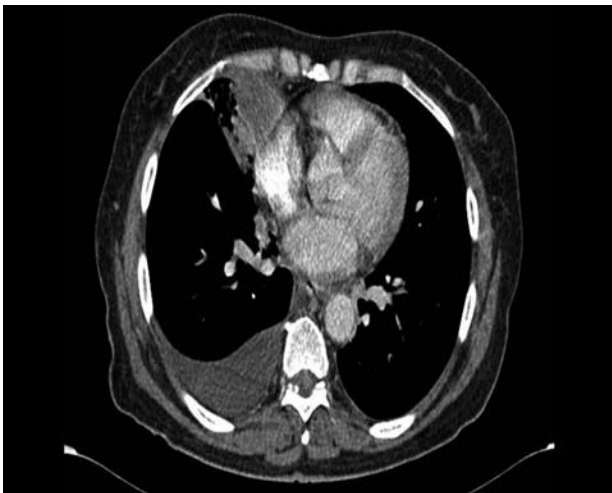


Figure 2. Computed tomography image showing the presence of a single mass in the lung.

of chronic nonproductive cough. During her stay, dactylitis was detected that had appeared 4 months previously.

There was a clearly defined violaceous and indurated area of increased thickness at the distal end of the first finger of the right-hand (Figures 1A and B). The patient presented no associated symptoms. No locoregional lymph node involvement was palpable and no skin lesions were encountered in the general examination.

Blood tests revealed normocytic anemia and normal biochemistry. An x-ray of the right hand ruled out underlying destruction of the bone.

Histopathology using hematoxylin-eosin-stain revealed infiltration of the lower dermis and subcutaneous cell tissue by atypical cells with marked nuclear pleomorphism distributed in a trabecular pattern (Figure 1C). The trabeculae were separated by bands of fibrous tissue with marked myxoid degeneration (Figure 1D). Immunohistology was positive for carcinoembryonic antigen, thyroid transcription factor-1, and cytokeratin (CK) 7 but negative for S-100, CK20, gross cystic disease fluid protein 15, and estrogen and progesterone receptors.

Secondary acral metastasis to an adenocarcinoma of unknown origin was diagnosed and computed tomography of the thorax was requested. This revealed the presence of a mass in the lung (Figure 2). A biopsy of the mass showed adenocarcinoma. During staging, metastases were detected in many other organs. The patient died 3 months after diagnosis.

Since the first description of acral metastases related to breast adenocarcinoma was described by Handley in 1906,³ new cases have helped epidemiological, clinical, and prognostic characteristics be established for this clinical manifestation.

Acral metastases are most often associated with lung cancer (30%), breast cancer (11%), and melanoma. This lesion, and all cutaneous metastases in general, tend to appear after a primary tumor has been diagnosed. Acral

Table 1. Immunohistochemical Markers Most Used in Differential Diagnosis of Metastatic Adenocarcinoma of Unknown Origin, Showing the Percentage of Cases That Tend to Prove Positive for Each Antibody According to Tumor Origin

| | GCDFP-15 (%) | ER (%) | PR (%) | WT-1 (%) | TTF-1 (%) | CA19-9 (%) | CA125 (%) | PSA (%) | CEA (%) |
|--------------|--------------|--------|--------|----------|-----------|------------|-----------|---------|---------|
| Breast | +70 | +60 | +40 | +7 | – | +6 | +13 | +32 | +57 |
| Ovarian | – | +50 | +20 | +86 | – | +60 | +80 | – | +40 |
| Endometrial | – | +70 | +95 | – | – | +85 | +94 | – | +15 |
| Endocervical | – | +20 | +4 | – | – | +33 | +62 | – | +60 |
| Colon | – | – | – | – | – | +85 | +10 | – | +99 |
| Stomach | – | – | – | – | – | +83 | +11 | – | +80 |
| Prostate | +15 | +45 | +60 | – | – | +6 | +2 | +96 | – |
| Lung | – | +3 | – | – | +90 | +80 | +20 | – | +90 |
| Thyroid | – | +46 | +35 | – | +74 | +27 | +10 | – | – |

Abbreviations: CEA, carcinoembryonic antigen; GCDFP-15, gross cystic disease fluid protein 15; ER, estrogen receptor; PR, progesterone receptor; PSA, prostate specific antigen; TTF-1, thyroid transcription factor 1; WT-1, Wilm tumor 1.

metastases appear in the hands in 62% of cases, although the low percentage of metastases to the feet is probably due to the lack of routine examination of this area.³⁻⁵

The clinical presentation of acral metastasis is of a clearly defined violaceous indurated mass, painless and not adherent to deep tissues, measuring between 5 mm and 6 cm in diameter, located on the distal phalanges or the back of the hands.⁵

Histologically, cutaneous metastases are characterized by the presence of a densely cellular infiltrate in the mid and deep dermis, occasionally extending into subcutaneous cellular tissue.⁶ This infiltrate is formed by atypical cells with a large number of mitosis. Immunohistochemical techniques can be considered alongside the form of presentation and radiological techniques to provide guidance on possible etiology in cases where the primary origin of the tumor is unknown⁷ (Table).

Differential clinical diagnosis must be used to rule out infectious processes such as cellulitis or atypical mycobacteriosis. These conditions tend to have less clearly defined erythema than cutaneous metastasis, and histology shows a predominantly inflammatory component. A positive culture is central to the diagnosis of any infectious process.

The prognosis for patients with lung cancer and cutaneous acral metastasis is poor, with a mean survival of 5 months, as these patients generally have advanced disease.^{6,8}

Treatment of acral metastases will vary from no treatment at all when there are no symptoms, to amputation of the digit in the case of a single lesion. Radiotherapy may be considered in the case of multiple lesions.

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