Interstitial Pattern of Cutaneous Metastases and Its Diagnostic Pitfalls: A Report of Three Cases

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Abstract

Cutaneous metastases are rare and indicate a poor prognosis. Occasionally, these may be the only presenting sign, with clinically inapparent primary source of the malignancy. Of the various histologic patterns of cutaneous metastases, interstitial pattern is very uncommon and mimics inflammatory diseases such as granuloma annulare. This article illustrates three such cases and underscores the role of morphology and immunohistochemical markers in establishing the correct diagnosis.

Keywords: Cutaneous metastases, granuloma annulare, interstitial pattern

INTRODUCTION

Skin, although the largest human organ, is not a very common site for harboring metastases from internal malignancies. The incidence of cutaneous metastases reported in literature varies from 0.6 to around 10.4%. While the index of suspicion may be high in a patient with documented malignancy, it is often unsuspected and may be the first sign. In such a case, the pathologist has to overrule a wide list of inflammatory conditions and take the help of ancillary techniques to prove its neoplastic nature. This report highlights three cases wherein clinically silent visceral malignancies were suggested based on the evaluation of cutaneous lesions.

Case Reports

Case 1

A 65-year-old woman presented with multiple indurated skin lesions, some showing ulceration, over the right side of the chest, back, shoulder, and axilla. The treating physician had differentials of Herpes zoster or possible metastatic disease. There was no palpable breast lump and no lung lesion on chest X-ray. A skin biopsy was done.

Histopathology showed the presence of neoplastic cells arranged in nodular as well as interstitial pattern [Figure 1a] in the dermis. The neoplastic cells were seen dissecting between collagen fibers [Figure 1b]. The epidermis was also involved in a Pagetoid manner, with nests of tumor cells [Figure 1a]. The cells showed glandular differentiation and were also present in cords and in an Indian file pattern. Marked nuclear atypia was noted, along with a few vascular emboli. There was a sparse plasma cell infiltrate in the dermis along with fibrosis. On immunohistochemistry, the cells were positive for pancytokeratin, cytokeratin-7 (CK-7) [Figure 1c], and gross cystic disease fluid protein-15 (GCFDP-15), which pointed toward an underlying breast malignancy.

Case 2

This was a 45-year-old man with multiple skin nodules over the left side of the neck and upper limb for 6 months. These nodules were gradually increasing in size. The patient also had low backache and bilateral hip pain over the same period of time. Local examination revealed lymphedema over the left side of the face, neck, and breast, with nipple retraction. There was no breast lump palpable and no breast lesion detectable on radiology. Magnetic resonance imaging of the spine showed cystic lesions in the spine which were very suspicious for metastases. The patient had a skin biopsy done from one of the neck nodules.

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The epidermis was uninvolved, and the dermis showed an interstitial infiltrate of cells arranged in cords and Indian file pattern [Figure 2a and b]. Minimal nuclear atypia was observed. There was a sparse lymphocytic infiltrate in the dermis. Keloidal collagen was noted [Figure 2a].

Immunohistochemistry showed positivity for pancytokeratin and CK-7 [Figure 2c]. Staining for GCDFP-15 was negative. The possibility of a primary neoplasm in the upper gastrointestinal tract, lung, or breast was suggested.

**Case 3**

A 57-year-old man presented with nodules over the scalp and supraclavicular region. Radiological examination showed cystic lesions in the skull, and the possibility of multiple myeloma was considered; the patient was subjected to further investigations. Both the scalp and supraclavicular nodules were biopsied. The laboratory workup for myeloma was negative.

This case also showed an unremarkable epidermis and an interstitial infiltrate of cells in cords and Indian file pattern [Figure 3a]. Cellular atypia was inconspicuous, and the cells were closely interspersed with lymphocytes and histiocytes [Figure 3b]. Keloidal collagen was noted.

The cells were positive for pancytokeratin and CK-7 [Figure 3c]. Positivity for GCDFP-15 was also seen in some cells. A possible primary in the breast or lung was suggested, but the patient deferred further investigations.

Interestingly, the second biopsy from case 3, which was a supraclavicular nodule, showed a dermatofibroma (DF) and no evidence of metastasis.

Tables 1 and 2 summarize the salient histological and immunohistochemical findings in all the three cases.

**Discussion**

The incidence of skin metastases, as reported in literature, varies from around 0.6% to 10.4%.\(^1\)\(^-\)\(^4\) Lung and breast, by far, form the most common sources of primary malignancies in men and women, respectively.\(^1\)\(^-\)\(^5\) Usual sites involved are head and neck and anterior chest in men, while in women, anterior chest and abdomen are the preferred sites.\(^1\) Most of these metastases are seen in late stages of disease and herald a poor prognosis. The median survival is reported to be as low as 6.5 months in patients with skin metastasis, with the worst survival rate in patients of lung carcinoma.\(^6\)\(^,\)\(^7\)

Clinically, cutaneous metastases may be seen as nodules, papules, plaques, tumors, or ulcers.\(^8\) Rare presentations include carcinoma en cuirasse, erysipelas-like, telangiectatic, and alopecia.\(^9\) In many instances, the histological finding of metastasis may be incidental and the underlying malignancy may actually not be apparent.\(^9\)\(^,\)\(^2\) Skin metastasis as the first manifestation of an internal malignancy is seen mostly in tumors arising from the lungs, kidneys, and ovaries.\(^10\)

Histologically, four patterns of cutaneous involvement have been described as follows: nodular, infiltrative (interstitial), diffuse, and intravascular.\(^8\) While the nodular and diffuse patterns are relatively easier to identify on morphology, it is the interstitial or the infiltrative pattern which poses a common diagnostic problem to the histopathologist.

In all the three cases in our series, the infiltrate was seen insinuating between bundles of collagen accompanied by lymphohistiocytes. An Indian file pattern was also discerned, where the cells were seen in a single-file-like linear pattern. This subtly differs from the interstitial pattern where a more dissecting or insinuating pattern in between collagen bundles was seen.
The most common inflammatory condition with this interstitial pattern is granuloma annulare (GA). Although classically described as an example of palisading granuloma, interstitial GA is more common in our experience. \(^{[11]}\) Two of our cases had negligible cytologic atypia, making GA a plausible diagnosis. Mucin is commonly found in GA and may be an additional confounding factor. This was not seen in our cases. Degenerative changes in collagen seen in GA have also been recorded in metastases. \(^{[12-14]}\) The clues that may help in distinguishing the two are a more cellular dermis and presence of atypia in the metastatic lesions. \(^{[13]}\)

Keloidal collagen was noted in two of three cases in this series. In combination with an interstitial infiltrate, this brings into play another common entity, DF. DF is characterized by interstitial or diffuse infiltrates of histiocytes with angulated fibroblasts and keloidal bundles of collagen at the periphery. The margins are ill-defined. There are a variable number of giant cells, siderophages, and foam cells that aid in the distinction. Another helpful clue is the phenomenon of induction of follicular/sebaceous structures in the epidermis overlying a DF. \(^{[15]}\) It is fortuitous that case 3 had a DF at a site different from the metastasis.

The first case showed epidermal involvement by tumor cells in a Pagetoid pattern. Alcaraz et al. observed this commonly in the perianal or genital skin. \(^{[8]}\) They prefer to designate these as epidermotropic metastases, in order to distinguish them from authentic extramammary Paget’s disease. They have been reported in carcinomas from breast, hypopharynx, and stomach. \(^{[9]}\)

In a patient with documented malignancy, the index of suspicion for metastases is higher. In all three of our cases, there was no known primary and we had to rely on ancillary diagnostic tests. Immunohistochemistry is a valuable tool that comes to the pathologist’s aid in these instances. \(^{[16]}\) Selection of markers should be based on malignancies common in particular age groups, sites, and geographic distribution. Two of our cases were positive for CK-7 and GCDFP, indicating that the likely primary was in the breast. The third case showed only CK-7 expression. The panel we have used is not exhaustive. The panel should also include markers for melanoma such as S100 and Melan-A. Desmoplastic melanoma is an important mimic.

Although rare, the classical form of epithelioid sarcoma can resemble cutaneous metastases both clinically and histologically, especially in cases with minimal cellular atypia. Demonstration of co-expression of CK and Vimentin stains, along with a positive stain for CD34, can distinguish these two entities in a majority of cases. \(^{[17]}\)

Immunohistochemistry not only helps in determining the possible primary tumor but also is useful to highlight morphologic patterns of the infiltrate and the depth of infiltration. These features may often be difficult to assess on histology due to the presence of a dense inflammatory component. Nevertheless, one has to keep in mind the

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**Table 1: Histological features noted in the skin biopsies**

| Histologic feature | Case 1                           | Case 2                           | Case 3                           |
|--------------------|----------------------------------|----------------------------------|----------------------------------|
| Epidermis          | Involved, pagetoid               | Normal                           | Normal                           |
| Ulceration         | Absent                           | Absent                           | Absent                           |
| Dermal pattern     | Nodular, interstitial            | Interstitial                     | Interstitial                     |
| Lymphovascular invasion | Present               | Absent                           | Absent                           |
| Tumor patterns     | Glands, cords, Indian file       | Cords, Indian file               | Cords, Indian file               |
| Inflammatory cell type | Sparse, plasma cells            | Sparse, lymphocytes              | Sparse, lymphohistiocytes        |
| Atypia/pleomorphism | Marked                           | Mild                             | Mild                             |
| Necrosis           | Absent                           | Absent                           | Absent                           |
| Dermal changes     | Fibrosis                         | Keloidal collagen                | Keloidal collagen                |

**Table 2: Results of panel of immunohistochemistry**

| IHC marker | Case 1 | Case 2 | Case 3 |
|------------|--------|--------|--------|
| Pan CK     | Positive, 95% | Positive, 95% | Positive |
| CK 7       | Positive, 90% | Positive, 90% | Positive, 40% |
| CK 20      | Negative | Negative | Negative |
| CD 68      | Scattered | Scattered | Scattered |
| GCDFP-15   | Positive, 20% | Negative | Positive, 30% |
| Ki 67      | Positive, 70% | Positive, <5% | Positive, 20% |
| CK 5/6     | Negative | Negative | Negative |
| TTF1       | Negative | Negative | Negative |
| CEA        | Negative | Negative | Negative |
| Possible primary | Breast | Upper GIT, salivary glands | Breast, lung |

CK: Cytokeratin, GCDFP: Gross cystic disease fluid protein, TTF-1: Thyroid transcription factor-1, CEA: Carcinoembryonic antigen, GIT: Gastrointestinal tract.
sensitivity and specificity of various markers selected and understand that a negative result does not completely exclude a diagnosis, which can be particularly vexing in unknown primary sites.

**Conclusion**

The interstitial pattern of cutaneous metastases on histology has a high likelihood of being mislabeled as an inflammatory condition. Careful histologic examination, appropriate clinical information, imaging, and prudent use of immunohistochemistry help in determining the probable primary source of malignancy in most cases. The overall patient survival may be poor, but pinpointing the possible primary can direct specific treatment modalities.

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**Conflicts of interest**

There are no conflicts of interest.

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