Zosteriform Cutaneous Metastases: A Literature Meta-Analysis and a Clinical Report of Three Melanoma Cases

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BACKGROUND Despite frequent skin involvement with solid tumors, zosteriform metastases are a rare, not well-defined entity, with only few cases published in literature. The unifying characteristic is merely topographic: cutaneous lesions were distributed along dermatomes, despite the variety of clinical features, including vesicobullous, papular, and nodular lesions. Several theories have been proposed to explain the pathogenetic mechanism of zosteriform dissemination, even if none was adequately proved.

OBJECTIVE In this article, we report three new cases of patients with melanoma with skin zosteriform metastases and present a meta-analysis of literature data.

METHODS AND MATERIALS We collected all Entrez-PubMed articles about zosteriform skin metastasis since 1970 and reviewed 56 cases, including our own taken from a 4,774-patient series.

RESULTS The histotypes mainly implicated were melanoma (18%); lymphoma (14%); breast cancer (12%); squamous cell carcinoma (12%); and digestive (10.7%), respiratory (10.7%), and urinary tumors (7%), with other histotypes accounting for 14%. In only one case in our series did we describe a typical herpetiform pattern, whereas in the others we found papulonodular lesions with a dermatomeric distribution.

CONCLUSION Cutaneous metastases with zosteriform pattern are rare and show a wide clinicopathologic spectrum that could affect the disease course.

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C utaneous metastases occur in approximately 5% to 10% of solid tumors,¹ in the late phases of disease progression as well as a first manifestation of malignancy. Breast cancer is the most commonly involved tumor, accounting for more than 60% of cases of cutaneous spreads, followed by colon carcinoma.² Malignant melanoma has also a high tendency to metastasize to the skin, whereas cutaneous metastases are relatively rare in patients with other cancer types, ranging from 0.6% to 10% depending on the different study series.^{1,3}

From a clinical point of view, the most common presentations of cutaneous metastatic disease are papules and nodules, solitary or widespread, sometimes ulcerated. However, a wide morphological spectrum of lesions has been described, including erythematous patches or plaques, inflammatory erysipela-like lesions, diffuse sclerodermiform lesions with induration of the skin ("en cuirasse" metastatic carcinoma), telangiectatic papulovesicles, purpuric plaques mimicking vasculitis, and alopecia areata—like scalp lesions.^{1,3–5} The so-called zosteriform pattern has been described in few cases; a recent meta-analyses reviewed 29 cases published in the English literature since 1970.⁶ The unifying feature seems to characterize this entity as merely topographic, with cutaneous lesions distributed along one or more dermatomes; on the other hand, various morphological features have been reported, including not only vesicobullous herpetiform lesions, but also papules and nodules. Several theories have been proposed in the literature to explain the pathogenetic mechanism of zosteriform dissemination, even if none was adequately proved.

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In this article, we report three additional cases of cutaneous melanoma metastases with a zosteriform pattern and present a meta-analysis of literature data on this topic. The aim is to detail this unusual morphological entity, identifying the predominant morphological pattern related to primary malignancy and to evaluate its effect on the clinical outcome.

Case Reports

Case 1

B.G., 72-year-old male. Primary melanoma on his left lumbar region (Clark level IV, Breslow thickness 16 mm, ulcerated) treated with wide surgical excision completed by sentinel lymph node biopsy. One month after, the patient underwent a new surgical treatment because of the development of two pericicatricial bluish infiltrated papules that microscopic examination confirmed as satellite metastases. In the following 3 months, new and numerous lesions developed in the left lumbar region, involving the left side of the chest and the abdomen, with a typical zosteriform distribution along the dermatomes corresponding to T2-T8 (Figure 1). The



Figure 1. Case 1: erythematous to bluish and dark infiltrated papules, papulonodules, and coalescent papulovesicles along the T2-T8 dermatomes.

lesions were erythematous to bluish and dark infiltrated papules, papulonodules, and coalescent papulovesicles, some with a crusted or ulcerated surface. Restaging revealed a secondary swelling of the left axillary nodes. Palliative chemotherapy was provided without benefit, and the patient died with massive visceral involvement 9 months after the initial diagnosis. Polymerase chain reaction (PCR) for herpes simplex virus (HSV)- and varicella zoster virus (VZV)-specific DNA sequences was performed on skin lesion samples, but no viral DNA amplification was detected. Serology for HSV I/II and VZV was negative. No history of previous zoster infection was known.

Case No. 2

A.B., 81-year-old male. Primary melanoma located on the right hip (Clark level III, Breslow thickness 6 mm) treated by wide surgical excision and sentinel node biopsy, followed by radical dissection of the right groin. Four months after, the patient developed local cutaneous relapses associated with inguinal node involvement. Despite palliative chemotherapy (cisplatin, fotemustine, dacarbazine) and radiotherapy, new brown to black papulovesicles and nodular lesions developed on his right side with the typical zosteriform distribution along the L1-L4 dermatomes, extending from the lumbar to the inguinal homolateral region (Figure 2). Also in this patient, laboratory tests for HSV/VZV infection were negative, and the patient did not refer to previous zoster infections. Disease metastasized to brain and bone, and the patient died 5 months after the occurrence of zosteriform metastases.

Case No. 3

B.M., 63-year-old male. Two primary melanomas located on his interscapular region (one Clark level IV, Breslow thickness 2 mm; one Clark level III, Breslow thickness 1.3 mm), both treated with wide surgical excision plus sentinel lymph node biopsy, followed by radical dissection of left axillary lymph nodes. One month after the first diagnosis, the patient developed multiple painless vesicular lesions



Figure 2. Case 2: brown to black papulovesicle and nodular lesions with the typical zosteriform distribution along the L1-L4 dermatomes.

with zosteriform distribution along the T4-T8 dermatomes (Figure 3). Patient had no history of previous VZV infection. PCR amplification failed to detect HSV DNA from skin lesions. Serology for HSV I/II and VZV was negative. Microscopic examination showed metastatic melanoma cells in these lesions. A computed tomography (CT) scan excluded visceral involvement, so the patient underwent a new radical surgical treatment of the cutaneous localizations. After a further relapse of several vesicular lesions on the same dermatomes, the patient was treated with monochemotherapy (dacarbazine), obtaining complete clinical remission. At the time of writing, the patient is alive, without visceral involvement, but with a new cutaneous zosteriform relapse.



Figure 3. Case 3: painless vesicular lesions with zosteriform distribution along the T4-T8 dermatomes. (a) A close-up of a vesicular lesion.

Literature Meta-Analysis

We collected all Entrez-PubMed articles about zosteriform skin metastasis since 1970, reviewing a total of 56 cases, including our own (Table 1). Both sexes were almost equally represented, with 29 (51%) males and 27 females (49%).

Regarding the histotype of primary malignant tumor, we found eight (14%) lymphomas (1 Hodgkin's lymphoma, 2 non-Hodgkin's lymphoma, 3 cutaneous B-cell lymphoma, 2 cutaneous T-cell lymphoma), seven (12%) breast cancer, seven (12%) squamous cell carcinomas (SCC), six (11%) digestive tumors (2 gastric, 3 colon, 1 gallbladder), six (11%) respiratory tumors (5 lung, 1 larynx), and four (7%) urinary tumors (2 kidney, 1 bladder, 1 prostate). Other histotypes (angiosarcoma, Kaposi's sarcoma, adnexal neoplasm, ovarian cancer, porocarcinoma, Ewing's sarcoma) accounted for 14%. Four patients

TABLE 1. Meta-analysis of Literature Cases since 1970

Author	Sex/ Age	Cancer	Time from First Diagnosis to Zosteriform Metastases	Site of Lesions	Vesico- (Bullous) Lesions	Metastatic Involvement	Survival (from Skin Involvement)
Bassioukas ⁷	F/54	Breast	3 months	Trunk (T4-T7)	No	Regional nodes	NA
Brasanac ⁸	F/54	Breast	13 years	Trunk, scalp	Yes	No	8 months
Torchia ⁹	F/71	Breast	Simultaneous	Trunk	Yes	No	NA
Williams ¹⁰	F/43	Breast	2 years	Trunk (T7)	No	Brain, bone	2 months
Manteaux ¹¹	F/48	Breast	2 years	Trunk	No	NA	Alive
Cecchi ¹²	F/78	Breast	6 years	Chest, back	Yes	No	8 months
Heckmann ¹³	F/62	Breast	8 years	Trunk, right side	No	Regional nodes	NA
Bauza ¹⁴	F/71	SCC (buttock)	Some months	Groin, buttocks, leg	No	NA	NA
Cohen ¹⁵	F/83	SCC (head)	5 months	Head	No	No	NA
Cuq-Viguier ¹⁶	F/83	SCC (arm)	NA	Trunk (T3-T5)	No	Regional nodes	1 month
Fearfield ¹⁷	M/56	SCC (trunk) HIV	<3 years	Chest, arm	Yes	Regional nodes	Few weeks
Kato ¹⁸	F/72	SCC (leg)	17 months	Trunk (L1-L3), hip, thigh	Yes	Regional nodes	NA
Buecker ¹⁹	M/65	SCC (chest)	2 years	Chest, arm	No	NO	Several weeks
Shafqat ²⁰	M/31	SCC (arm)*	6 years	Chest	No	Regional nodes	Alive
Kikuchi ²¹	M/53	Gastric	3 years	Left abdomen, flank (T10)	Yes	Peritoneum	4 months
Kikuchi ²¹	F/63	Gastric	4 months	Trunk (T3)	No	Regional nodes	2 months
Maeda ²²	M/65	Colon	5 years	Thigh (L1–L3)	Yes	Regional nodes, peritoneum	5 months
Damin ²³	F/44	Colon (rectum)	6 months	Groin, abdomen	No	NO	3 months
Ahmed ²⁴	M/79	Colon	3 years	Chest, arm (T2–5)	Yes	Regional nodes	Few weeks
Kamisawa ²⁵	M/84	Gallbladder	4 years	Trunk (T6-T8)	Yes	Regional nodes, lung	4 months
Shamsadini ²⁶	M/58	Larynx	9 months	Shoulder	Yes	NA	NA
LeSueur ²⁷ Hodge ²⁸	F/66	Lung	1 year	Thigh, groin	No	Non-regional nodes, bone	NA
Matarasso ²⁹	M/57	Lung	Three weeks 5 months	Trunk (T5-T7)	Yes	Regional nodes NO	4 months Alive
Bianchi ³⁰	M/65 M/71	Lung Lung	Simultaneous	Trunk (T7) Lower face	No No	Pleural, lung	3 weeks
Kikuchi ²¹	M/69	Lung	Some months	Trunk (T8-T9)	No	NA	1 month
Martinez ³¹	M/85	Melanoma (primary unknown)	Simultaneous	Buttocks, hip, leg (L1-L2)	No	NA	1 month
Zalaudek ³²	F/59	Melanoma (4 mm back)	2 years	Trunk, back (D7-D9)	No	Regional nodes	NA
Stern ³³	F/53	Melanoma	NA	Forearm	NA	NA	1 year
ltin ³⁴	F/29	Melanoma (2.3 mm back)	< 5 months	Trunk (T5)	No	Regional nodes	17 months
North ³⁵	M/63	Melanoma (5mm preauricular)	5 years	Trunk (T12)	Yes	Regional nodes	3 months
Kondras ³⁶	M/65	Melanoma (11 mm back)	2 months	Back	Yes	Regional nodes	NA
Galindo ³⁷	M/79	Melanoma (4 mm chest)	11 months	Chest (T6)	No	No	NA
Evans ³⁸	M/73	Melanoma (1.25 mm shoulder)	5 years	Scalp	Yes	NA	NA
Number 1 †	M/72	Melanoma (16mm lum- bar region)	3 months	Chest (T2-T8)	Yes	Regional nodes	6 months
Number 2^{\dagger}	M/81	Melanoma (6mm right hip)	4 months	Trunk (L1-L4)	Yes	Regional nodes	5 months
Number 3 [†]	M/63	Melanoma (2 mm and 1.3 mm interscapular region)	1 month	Chest (T4-T8)	Yes	Regional nodes	Alive (>3 years)

TABLE 1. Con	unueu						
Author	Sex/ Age	Cancer	Time from First Diagnosis to Zosteriform Metastases	Site of Lesions	Vesico- (Bullous) Lesions	Metastatic Involvement	Survival (from Skin Involvement)
Hudson ³⁹	F/57	Angiosarcoma	Contemporary	Head (C3)	No	NA	Alive (>2 years)
Niedt ⁴⁰	M/31	Kaposi HIV	4 months	Chest (T3)	No	NA	10 weeks
Roth ⁴¹	M/42	Kaposi HIV	NA	Leg	No	Regional nodes	NA
Patsner ⁴²	F/70	Ovary	6 weeks	Thigh, groin	No	NA	NA
Schonmann ⁴³	F/48	Ovary	3 years	Lower abdomen, buttocks, thigh	Yes	Peritoneum, bladder	<3 months
Garcia-Mo- rales ⁴⁴	M/57	Hodgkin	Contemporary	Trunk, axilla	Yes	Regional nodes	Few weeks
Au ⁴⁵	M/72	Non-Hodgkin lymphoma	NA	Trunk (T6)	Yes	No	Alive
Niiyama ⁶	F/77	Non-Hodgkin lymphoma	1 month	Trunk (T4–5)	No	Regional nodes	5 months
Torne ⁴⁶	M/54	Cutaneous B-cell Iymphoma	NA	Trunk (T10–11)	No	NA	Alive
Aloi ⁴⁷	F/77	Cutaneous B-cell Iymphoma	2 years	Trunk (T7–8)	No	NA	Alive
Watabe ⁴⁸	M/86	Cutaneous B-cell lymphoma	NA	Abdomen	No	NA	Alive
Williams ⁴⁹	M/86	Cutaneous T-cell lymphoma	Contemporary	Neck, shoulder	No	NA	6 months
Ricci ⁵⁰	F/66	Cutaneous T-cell lymphoma	2 years	Thorax	Yes	NO	Alive
Akiyoshi ⁵¹	F/78	Cutaneous poro- carcinoma (buttocks)	6 months	Buttock, hip	No	Regional nodes	Alive (>16 months)
Manteaux ¹¹	F/80	Adnexal	5 months	Trunk (T12-L1)	Yes	NA	Several months
lzquierdo ⁵²	F/40	Ewing sarcoma (forearm)	<6 months	Upper limb	Yes	Regional nodes, lung, bone	> 8 months
Woodruff ⁵³	F/63	Bladder	1 year	Lower abdomen, pelvis (T12-L1)	No	NA	NA
Ando ⁵⁴	M/67	Kidney	3 years	Chest	No	Regional nodes	Alive (>10 months)
Bellman ⁵⁵	M/67	Prostate	7.2 years	Lower abdomen	No	Bones	NA

*Transplant recipient.[†]Cases 1, 2, and 3 reported in the current study.

TABLE1 Continued

NA = not available; HIV = human immunodeficiency virus; SCC = squamous cell carcinoma.

with zosteriform cutaneous metastases were infected with the human immunodeficiency virus (HIV) or were transplant recipients. From the clinical point of view, 25 (45%) patients had a vesicular pattern, whereas in the remaining cases, a prevalence of papulonodular lesions arranged along one or more dermatomes was observed. Vesicular lesion were present in three of the seven (42%) breast cancers, two of the seven (28%) SCCs, one of the five (20%) lung cancers, one of the two (50%) gastric cancers, and two of the three (66%) colon cancers; six of the 10 patients with melanoma cases showed a vesicular pattern (60%). Serology or PCR amplification for HSV I/II and VZV showed a history of previous viral infection in seven patients. No previous herpes infection was demonstrated in 12 patients.

Cutaneous melanomas account for 19.6% (11/56) of zosteriform metastases reported in the literature. The

mean Breslow thickness was 5.28 mm, with a prevalence of male patients (8/10) and primary lesion localized mainly on the trunk. Zosteriform localizations usually arise in the same body region of the primary melanoma.

Time from melanoma excision and diagnosis of zosteriform metastases was a random variable: in only one case was the diagnosis made at the same time, whereas in all other patients, it ranged from 1 month to 5 years (mean 6.1 months). The overall patient outcome was poor, with a mean survival from skin involvement of 11.2 months (range 1-36 months).

Discussion

Skin metastases from solid tumors are a relatively frequent appearance of disease progression, with an incidence ranging from 5% to $10\%^1$ and a highly variable clinical spectrum. However, cutaneous metastases with a zosteriform distribution are rare. To the best of our knowledge, only 56 cases, including our own three, have been reported in the literature since 1970.

The histotype of primary malignant tumor was various, with a relevant percentage of hematological malignancy and breast and skin carcinomas.7-20,44-50 Melanoma accounted for 19.6%, justifying the larger series of zosteriform metastases reported to date, with 11 of 56 cases described so far.³¹⁻³⁸ However, the prevalence of zosteriform metastases is lower than that of cutaneous melanoma localizations. Also, in our series of 4,774 patients with melanoma, we observed 424 cases of skin metastases as the first site of relapse, with only three of them with a zosteriform pattern (0.7%). All of these melanoma cases had similar clinical features: thick melanoma, localized mainly on the trunk; regional lymph node involvement together or before the zosteriform spreading; development on a site near the primary melanoma; and poor prognosis (<12 months from the diagnosis of zosteriform metastases). However, the morphology of the cutaneous

lesions had remarkable dissimilarities. Only a few authors^{36,38} described metastases as painful and pruritic vesicles on a background of erythema, with a herpetiform appearance; the majority of them use the term "zosteriform" based only on dermatomeric distribution of lesions, even if they appear as pigmented papulonodes.^{31,32,34} On the other hand, there are reports in the literature of vesicular melanoma metastases not restricted to a single dermatome.^{56,57}

Our patients confirm the presence of two different clinical patterns; we observed a pure typical vesicular pattern in only one case (case 3), whereas in the others (case 1 and 2), papules, nodules, and vesicles coexisted, with a polymorphic appearance.

However, along the clinical course, vesicles could evolve into solid lesions. The morphology of the cutaneous involvement may change depending on biological behavior and the time of diagnosis. In our experience, one patient (no. 3) showed persistence of a vesicular pattern, despite repeated relapses of treated lesions; the clinical course was favorable, and the patient suffered only skin metastases, without signs of visceral progression after 3 years from the first diagnosis of cutaneous involvement. On the other hand, in the other two patients, we observed a rapid transition of vesicles into coalescent papulonodular lesions. In these cases, disease was aggressive, with early lymph node and visceral involvement, and both patients died within a few months after the diagnosis.

Unfortunately, published data about zosteriform melanoma metastases^{31–38} are too scanty and incomplete to minutely define this entity. However, for patients with melanoma with zosteriform metastases, an accurate medical history could be of primary importance for the right classification of the disease and for treatment choice. Moreover, clinicians treating oncology patients should consider this rare form of cutaneous involvement in the differential diagnosis of herpes zoster to avoid inadequate therapy and a dangerous delay in starting a correct treatment.

Zosteriform cutaneous metastases have been previously described in transplant recipients²⁰ and patients infected with HIV;^{17,40,41} however, our review of the literature shows that the majority of patients are HIV negative. Our clinical experience confirms these observations, even if the potential immunosuppressive role of chemotherapy remains to be established.

Several theories have been proposed to explain the mechanism of the zosteriform distribution of metastases, even if its pathogenesis remains unknown. Some of the patients described in the literature had a history of a zoster infection in the same dermatome in which metastatic lesions were subsequently observed.^{7,28,32,39,40,46,47} In these cases, zosteriform pattern could be a consequence of a Koebner or Koebner-like phenomenon in a site of diminished resistance of the skin.^{32,39,40} More recently, it has been suggested that neural alteration caused by the herpes virus resulted from an impairment of the immunological function of the overlying skin⁵⁸ that, consequently, could be more receptive to metastatic cell homing. Several authors showed evidence of viral DNA from skin of patients with zosteriform metastases,^{7,28,32,39,40,46,47} although PCR failed to detect the presence of HSV or VZV DNA in our patients, and they did not refer to previous VZV infections.

Other possibilities to explain how tumor cells spread with a zosteriform pattern include a direct invasion from underlying structures (in the case of internal cancer),¹⁴ surgical implantation of neoplastic cells into the skin,⁵⁹ and invasion of perineural lymphatic vessels or of the dorsal root ganglion fenestrated vasculature. The clinical evidence, reported by several authors, of tissue swelling and the histopathologic demonstration of enlarged lymphatic vessels with focal neoplastic embolism supports the hypothesis of metastatic spread through the lymphatic system;^{7,25,27} widespread lymphatic obstruction by tumor cells can result in retrograde flow that spreads malignant cells into the skin.³⁶ In our opinion, this last hypothesis seems more apt to describe the pathogenesis of zosteriform metastases in patients of our series. In fact, all these patients demonstrated involvement of regional lymph nodes, with concomitant development of cutaneous metastases.

In summary, cutaneous metastases with zosteriform pattern are rare entities, with various clinical, morphological, and histopathologic backgrounds that could affect the clinical course of disease. This article tries to better characterize this entity and provide three new melanoma cases to the literature.

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