

Erythema Nodosum-like Panniculitis Associated with the Use of Vemurafenib

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Abstract

Melanoma a type of skin cancer derived from melanocytes which represents around 4% of all skin cancers recorded till date, but is responsible for 80% deaths due to skin tumors. The development of new targeted therapies directed specifically against malignant cells has brought hope to the treatment of melanoma patients. The first drugs developed against specific molecules were BRAF inhibitors, designed for the treatment of metastatic melanoma. These drugs have been demonstrated to improve both overall and disease-free survival in these patients. At the same time, a wide range of adverse events (AEs) have emerged from their use. Some of them are quite frequent and are observed regularly in everyday practice on the other hand, there are rare AEs that require an early diagnosis for adequate treatment so knowledge of their existence is crucial for timely recognition and patient management. We here have presented a case of erythema nodosum-like septal panniculitis in a patient receiving therapy with vemurafenib and cobimetinib.

Keywords: Melanoma; BRAF inhibitors; Vemurafenib; Adverse events; Erythema nodosum; Panniculitis

Introduction

Melanoma is a type of skin cancer derived from melanocytes, whose incidence has grown during the last decade. Even though it represents only 4% of all skin cancers, it is responsible for 80% of deaths from skin tumors and one of the most important in terms of years of potential life lost [1]. However, the development of new targeted therapies directed specifically against malignant cells has brought hope to the treatment of melanoma patients. The first drugs developed against specific molecules were BRAF inhibitors, designed for the treatment of metastatic melanoma with positivity for V600E BRAF mutation, which occurs in 40-60% of melanomas, especially in those arising in areas without chronic sun exposure [2]. These drugs have been demonstrated to improve both overall and disease-free survival in these patients [3]. At the same time, a wide range of adverse events (AEs) have emerged from their use. We must be familiar with these AEs since they can cause significant morbidity and even force discontinuation of therapy. Some of them are quite frequent and are observed regularly in everyday practice, such as maculopapular rash, photosensitivity, xerosis, keratosis pilaris or epithelial neoplasms [4]. On the other hand, there are rare AEs that require an early diagnosis for adequate treatment, so knowledge of their existence is crucial for timely recognition and patient management. Examples of these are neutrophilic dermatosis such as Sweet syndrome, eccrine neutrophilic hydradenitis and neutrophilic panniculitis [5]. We present a case of erythema nodosum-like septal panniculitis in a patient receiving therapy with vemurafenib and cobimetinib.

Case Report

A 43-year-old male was diagnosed with melanoma of unknown primary after consulting for a painful right axillary lymphadenopathy. Fine needle aspiration biopsy of the lymphadenopathy demonstrated epithelioid melanoma metastatic cells. Complete study of the patient revealed no signs of primary melanoma but detected left inguinal adenopathies, two lung metastases and one splenic metastasis. The patient started on combined therapy with vemurafenib and cobimetinib.

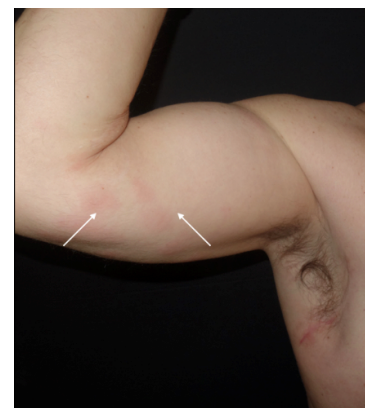


Figure 1: Subcutaneous nodules on the proximal upper and lower extremities.

One month later, the patient consulted in the Emergency Department for asthenia, malaise, high fever, and arthralgias that did not improve with non-steroidal antiinflammatory drugs (NSAIDs). Physical examination revealed infiltrated, erythematous, ill-defined

and painful subcutaneous nodules on the proximal upper (Figure 1) and lower extremities. They were also present to a lesser extent in the abdomen. A punch biopsy was performed and the patient was treated with oral prednisone 45 mg daily, with discontinuation of therapy for melanoma.



Figure 2: Findings characteristic of Miescher's granulomas.

Histological examination demonstrated a discrete superficial and deep perivascular inflammatory dermal infiltrate, associated with a dense neutrophilic infiltrate in the subcutaneous tissue septa, which in

some areas extended partially into the lobules. There were multiple granulomatous-like structures composed by histiocytes encircling a clear central space and surrounded by a dense neutrophilic infiltrate, findings characteristic of Miescher's granulomas (Figure 2).

The patient's symptoms and lesions resolved 2 weeks later, so steroid therapy was tapered down. One month later, both vemurafenib and cobimetinib were reintroduced, with subsequent reappearance of the same lesions. Adequate control was achieved with low-dose prednisone without requiring discontinuation of vemurafenib or cobimetinib.

Discussion and Conclusion

Neutrophilic panniculitis is a rare AE of BRAF inhibitor therapy, drugs used to treat metastatic melanomas with BRAF gene mutation. This type of panniculitis has also been described in children and adolescents with central nervous system tumors treated with vemurafenib [6]. So far, there have been over 20 cases reported of panniculitis associated with the use of BRAF inhibitors in metastatic melanoma (Table 1). This AE is mostly reported with BRAF inhibitors as monotherapy, and among these, it is more frequent with vemurafenib than dabrafenib. It has not been described in patients receiving MEK inhibitors exclusively. A recent report described a case of panniculitis associated to combined therapy with vemurafenib and cobimetinib that resolved and relapsed with the latter's removal and reintroduction, respectively [7]. This might be the first case of panniculitis associated to MEK inhibitor therapy, though it may also be a coincidental observation, as the majority of case reports describe resolution of lesions, either spontaneously or with NSAIDs, without discontinuation of BRAF inhibitor therapy.

Authors	Gender, Age (years)	Melanoma type (location of metastases)	BRAF _i ± other	Symptoms	Time of BRAF _i therapy until onset	Systemic symptoms	Histology (type of panniculitis)	Treatment	BRAF _i discontinuation	Course
Maldonado-Seral et al. [14]	F, 42	SSM (lung)	V	Nodules in legs	2 weeks	No	Lobular, neutrophilic and histiocytic	None	No	Resolution in a few days
Monfort et al. [15]	F, 70	ALM (lung, mediastinum, abdomen, central nervous system, subcutaneous, lymph node)	V	Painful nodules in legs	15 days	No	Neutrophilic	None	No	Resolution in 15 days
Monfort et al. [15]	F, 38	¿? (subcutaneous, lymph node, parotid, lung)	V	Painful nodules in arm	10 days	Arthralgias	Lobular neutrophilic panniculitis, deep neutrophilic dermatitis		No	Resolution in 5 days, some relapses
Zimmer et al. [11]	F, 44	MUP (lymph node, lung, mesentery, bone)	V	Painful nodules in arms, legs and gluteus	16 days	Generalized arthralgias	Lobular neutrophilic panniculitis, small vessel vasculitis	Prednisolone 1 mg/kg, indomethacin, dipyrene	Yes	Resolution in 11 days, reintroduction of V at 25% dose, relapse of arthralgias 5 days later, but no

										subcutaneous nodules
Zimmer et al. [11]	F, 59	ALM (lymph node, lung, liver, bone)	V	Painful nodules in arms and legs	7 days	Mild arthralgias	Septolobular neutrophilic panniculitis	Etoricoxib	No	Resolution in 4 weeks
Shina et al. [10]	F, 45	¿?	V	Painful nodules in arms and legs	37 days	Rash (Grade 3), arthralgias, conjunctivitis, photoensitivity	Erythema nodosum-like panniculitis	Analgesics	Yes (3-4 days)	Spontaneous resolution, reintroduction of V at 35% dose
Shina et al. [10]	M, 26	¿?	V	Painful nodules in arms and legs	31 days	No	Erythema nodosum-like panniculitis	None	Yes (3-4 days)	Spontaneous resolution
Kim et al. [16]	F, 52	¿? (lymph node)	V	Erythematoviolaceous plaques in legs	2 weeks	Arthralgias	Lobular neutrophilic panniculitis	None	No	Spontaneous resolution in months
Choy et al. (series of 9 patients, one initially D and later D + T) [8]	4F, 5M, mean 39 (29-71)	¿?	4V 3D 3D+T	Erythematous nodules in legs, arms and trunk	Mean 48 days (3-195 days)	Arthralgias (7 of 9 patients)	8 biopsies of 7 patients: 5 lobular panniculitis (4 neutrophilic, 1 lymphocytic, mixed). 3 mixed panniculitis (one with vasculitis)	None or NSAIDs. Oral prednisone in 3 patients	No	Complete resolution
Ramani et al. [3]	F, 50	ALM (lung, lymph node)	D	Nodules in legs and arms	8 weeks	No	Lobular neutrophilic panniculitis, necrotizing granulomas	Doxycycline 2 weeks	No	Resolution in 2 weeks, at 8 weeks disease progression (cerebral metastases) and exitus
Weng et al. [12]	F, 75	MUP (lymph node, mediastinum, lung)	V	Painful erythematous nodules in legs, arms and abdomen	1 week	No	Mixed neutrophilic panniculitis	Prednisone and celebrex	Dose reduction (halved)	Resolution in 5 weeks. After increasing dose, relapse of lesions, with subsequent dose reduction (halved)
Ferreira J et al. [17]	F, 35	Nevoid MM (lung, bone, liver, central nervous system)	V	Painful nodules in legs	6 weeks	No	Lobular neutrophilic panniculitis	Oral and topical corticoids	No	Complete resolution, no relapses
Ferreira J et al. [17]	F, 65	SSM (lung, skin)	V	Painful nodules in arms and legs	10 days	Fever, arthralgias, rash	Lobular neutrophilic panniculitis, foci of necrosis and apoptosis	None	Dose reduction	Complete resolution

F: Female; M: Male; BRAFi: BRAF inhibitor; V: Vemurafenib; D: Dabrafenib; T: Trametinib; SSM: Superficial spreading melanoma; ALM: Acral lentiginous melanoma; MUP: Melanoma of unknown primary

Table 1: Cases of panniculitis as associated to the use of BRAF inhibitors in patients with metastatic melanoma reported in the literature.

BRAF inhibitor-associated panniculitis is over two times more frequent in females than in males, and among patients treated with vemurafenib, it is more common in those with lung metastases. However, this last observation might be due to the high frequency of metastases in this location and have no pathogenic link to the development of panniculitis.

The majority of cases reported appeared early during therapy, between the 2nd and 3rd weeks of treatment. In the case series reported by Choy et al. lesions appeared later on (mean 48 days, range 3-195 days) [8]. Clinical presentation simulates erythema nodosum, with painful, erythematous nodules predominantly on the anterior aspect of the legs, although arm involvement is also frequent. They may be accompanied by systemic symptoms, usually with fever and arthralgias, in up to 60% of cases. Differential diagnosis should include subcutaneous metastasis of melanoma, so skin biopsy is required [8,9].

Histologic examination of reported cases reveal heterogeneous characteristics. These panniculitis are predominantly lobular and are composed of a neutrophilic infiltrate. Mixed septolobular panniculitis have been described in 4 patients, though the cases reported by Shina, et al. presented erythema nodosum-like panniculitis, similar to our case [10]. Pathology of our patient's lesions demonstrated a predominantly septal panniculitis, a dense neutrophilic infiltrate and multiple Miescher's radial granulomas. Though these are not pathognomonic, they are very typical of early erythema nodosum lesions. This is the first report of BRAF inhibitor-associated neutrophilic panniculitis with these histopathological findings.

These lesions usually resolve in a few days without requiring discontinuation of BRAF inhibitor therapy. However, as in our case, relapses after resuming therapy or increasing dose have been reported [11,12]. Treatment is symptomatic and usually analgesics and NSAIDs suffice, though some cases may require systemic corticosteroids, as did our patient. Some authors recommend using oral corticosteroids as initial treatment due to the intense pain these lesions can cause, which might even motivate discontinuation of therapy [13]. Each individual case must be carefully assessed before making the decision to interrupt BRAF inhibitor therapy [14].

In conclusion, we present a new case of BRAF inhibitor-associated erythema nodosum-like panniculitis presenting in a patient receiving combined therapy with vemurafenib and cobimetinib. Though the patient experienced a relapse after reintroducing therapy, avoiding a second discontinuation was possible due to adequate control with low-dose oral prednisone.

References

- Silva JH, de Sá BCS, de Ávila ALR, Landman G, Neto JPD (2011) Atypical mole syndrome and dysplastic nevi: identification of populations at risk for developing melanoma-review article. *Clinics* 66: 493-499.
- Besaratinia A, Pfeifer GP (2008) Sunlight ultraviolet irradiation and BRAF V600 mutagenesis in human melanoma. *Hum Mutat* 29: 983-991.
- Ramani NS, Curry JL, Kapil J, Rapini RP, Tetzlaff MT, et al. (2015) Panniculitis With Necrotizing Granulomata in a Patient on BRAF Inhibitor (Dabrafenib) Therapy for Metastatic Melanoma. *Am J Dermatopathol* 37: 96-99.
- Gençler B, Gönül M (2016) Cutaneous Side Effects of BRAF Inhibitors in Advanced Melanoma: Review of the Literature. *Dermatol Res Pract* 5361569.
- Herms F, Franck N, Kramkimel N, Fichel F, Delaval L, et al. (2017) Neutrophilic eccrine hidradenitis in two patients treated with BRAF inhibitors: a new cutaneous adverse event. *Br J Dermatol* 176: 1645-1648.
- Finelt N, Lulla RR, Melin-Aldana H, Ruth JS, Lin FY, et al. (2017) Bumps in the Road: Panniculitis in Children and Adolescents Treated with Vemurafenib. *Pediatr Dermatol* 34: 337-341.
- Negulescu M, Deilhaes F, Sibaud V, Tournier E, Lamant L, et al. (2017) Panniculitis Associated with MEK Inhibitor Therapy: An Uncommon Adverse Effect. *Case Rep Dermatol* 9: 80-85.
- Choy B, Chou S, Anforth R, Fernández-Peñas P (2014) Panniculitis in patients treated with BRAF inhibitors: a case series. *Am J Dermatopathol* 36: 493-497.
- Chaminade A, Conte H, Jouary T, Fauconneau A, Darrigade A-S, et al. (2015) BRAF inhibitors-induced panniculitis: a cutaneous side effect mimicking subcutaneous melanoma metastasis. *J Eur Acad Dermatol Venereol* 29: 392-393.
- Sinha R, Edmonds K, Newton-Bishop J, Gore M, Larkin J, et al. (2013) Erythema nodosum-like panniculitis in patients with melanoma treated with vemurafenib. *J Clin Oncol* 31: e320-321.
- Zimmer L, Livingstone E, Hillen U, Dömkes S, Becker A, et al. (2012) Panniculitis with arthralgia in patients with melanoma treated with selective BRAF inhibitors and its management. *Arch Dermatol* 148: 357-361.
- Weng YC, Chiu CS, Lin TH, Shen JL, Yang CS, et al. (2016) Vemurafenib-associated neutrophilic panniculitis in a patient with metastatic amelanotic melanoma presenting as cancer of unknown primary origin. *Dermatol Sin* 34: 88-91.
- Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A (2015) Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *J Am Acad Dermatol* 72: 221-238.
- Maldonado-Seral C, Berros-Fombella JP, Vivanco-Allende B, CotoSegura P, Vazquez-Lopez F, et al. (2013) Vemurafenib-associated neutrophilic panniculitis: An emergent adverse effect of variable severity. *Dermatol Online J* 19: 16.
- Monfort J-B, Pagès C, Schneider P, Neyns B, Comte C, et al. (2012) Vemurafenib-induced neutrophilic panniculitis. *Melanoma Res* 22: 399-401.
- Kim GH, Levy A, Compoginis G (2013) Neutrophilic panniculitis developing after treatment of metastatic melanoma with vemurafenib. *J Cutan Pathol* 40: 667-669.
- Ferreira J, Toda-Brito H, Moura MC, Sachse MF, Costa-Rosa J (2017) BRAFi-associated panniculitis - an emerging side effect with a variable histological picture: report of two cases and review of the literature. *J Cutan Pathol* 44: 307-309.