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## BRIEF COMMUNICATION

# Granulomatous Reaction in a Patient With Metastatic Melanoma Treated With Ipilimumab: First Case Reported With Isolated Cutaneous Findings<sup>☆</sup>



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### KEYWORDS

Anti-CTLA4;  
Immunotherapy;  
Metastatic melanoma;  
Sarcoidosis;  
Granulomatous reaction;  
Immune-related adverse event;  
Adverse drug reaction

### PALABRAS CLAVE

Anti-CTLA 4;  
Inmunoterapia;  
Melanoma metastásico;  
Sarcoidosis;  
Reacción granulomatosa;

**Abstract** Granulomatous sarcoidosis-like reactions affecting multiple organ systems at one time have infrequently been described within weeks to months after initiation of Ipilimumab. We present the first case of a 67-year-old man with isolated cutaneous granulomatous reaction involving the trunk, extremities, and face after eighteen months of treatment with ipilimumab for metastatic melanoma. This case documents the eruption of isolated cutaneous granulomatous reaction as a late treatment-related adverse effect of ipilimumab, highlighting the importance of adequate, prolonged follow-up.

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### Reacción granulomatosa en paciente con melanoma metastásico tratado con ipilimumab: primer caso descrito presentando clínica cutánea únicamente

**Resumen** Las reacciones granulomatosas «sarcoidosis-like» secundarias a ipilimumab afectarán simultáneamente a múltiples órganos y característicamente se presentarán semanas o meses después de haber iniciado el tratamiento. Paciente varón de 67 años, quien consulta por reacción cutánea granulomatosa a nivel de tronco, extremidades y rostro. Esta se presentó 18 meses después de haber iniciado tratamiento con ipilimumab, medicamento pautado por el diagnóstico de un melanoma metastásico. Reportamos reacción granulomatosa de presentación

<sup>☆</sup> Please cite this article as: Cervantes J, Rosen A, Dehesa L, Dickinson G, Alonso-Llamazares J. Granulomatous Reaction in a Patient With Metastatic Melanoma Treated With Ipilimumab: First Case Reported With Isolated Cutaneous Findings. Actas Dermosifiliogr. 2019;110:43–49.

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Evento adverso  
relacionado  
inmune-mediado;  
Reacción adversa  
medicamentosa

exclusivamente cutánea, como efecto adverso medicamentoso tardío secundario al tratamiento con ipilimumab. Así mismo resaltamos la necesidad de realizar en los pacientes tratados con ipilimumab un seguimiento prolongado.

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## Case History

A 67-year-old man attended the dermatology clinic for mild generalized pruritus with onset 6 months earlier, accompanied by multiple coalescent papular lesions that had presented initially on the back but subsequently spread rapidly to the face, arms, legs, backs of the hands and feet, groin, and hips. Of note in his medical history was diagnosis of metastatic melanoma (stage IV). The primary tumor had been diagnosed in the lumbar skin and the patient had metastases to the lung, liver, and retroperitoneal lymph nodes. Treatment with ipilimumab had induced complete remission for 2 years. Ipilimumab was administered initially at high doses (10 mg/kg) every 3 weeks for 4 cycles (induction phase) and then with a regimen of infusion every 3 months (maintenance phase). Dry skin, alopecia, and vitiligo were reported as adverse drug reactions to ipilimumab. All these were grade 1 and so no dose reductions were required. In addition to ipilimumab, the patient also received treatment with venlafaxine, olmesartan, fexofenadine, and ranitidine. He had no known drug allergies.

Physical examination revealed multiple inflammatory grouped papules with a crusty appearance, distributed symmetrically on the face (predominantly in the nasolabial folds, supraorbital arches, and glabella) (Fig. 1a) and on the neck, ears, scalp, groin, back, hips (Fig. 1b), elbows, wrists, and ankles (Fig. 1c). In the laboratory analysis including blood chemistry, hematology, urinary calcium, and angiotensin converting enzyme, parameters were within normal range. Cultures for mycobacteria, bacteria, and fungi were negative, as were purified protein derivative and rapid plasma reagin tests. Chest X-ray and computed tomography-positron emission tomography (CT-PET) did not show any pathological findings.

It was decided to obtain a biopsy of the lesions. Pathology study showed presence of nodular epithelioid granulomas surrounded by T lymphocytes in the dermis. In addition, areas were observed with lymphocytic epidermotropism, consistent with granulomatous dermatitis (Fig. 2a and b). Limited CD20+ B lymphocytes were detected, while CD39, CD56, CD1a, and S100 were negative. CD58 was positive for giant cells and also for some macrophages. Most of the lymphocytes of the infiltrate were marked with CD3, CD4, and CD7. The CD4:CD8 ratio was 2:1. Periodic acid-Schiff, Gomori methenamine silver, Giemsa, gram, and Fite stains were negative. Specific stains for *Treponema* were also negative.

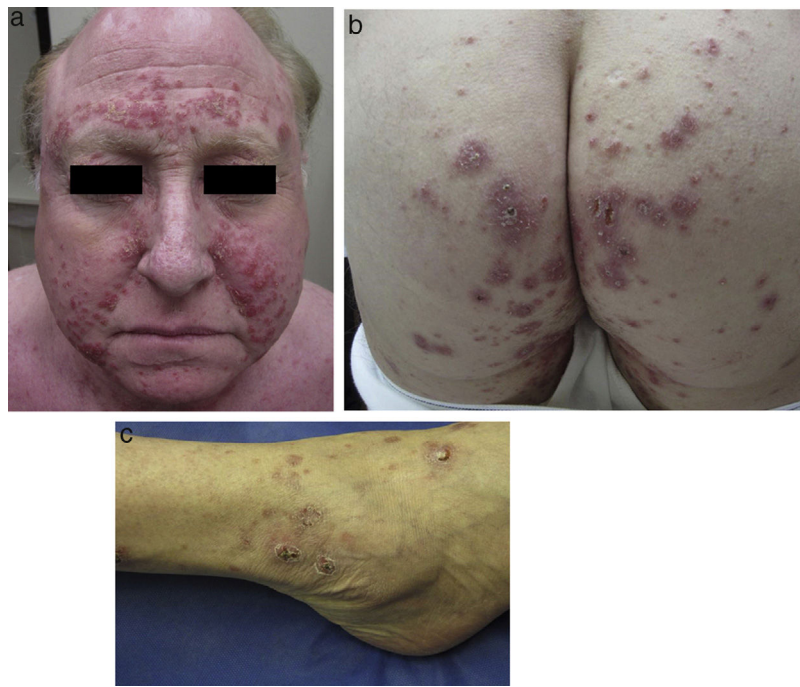
In view of these clinical and histological findings, granulomatous dermatitis induced by ipilimumab was diagnosed. Treatment was initiated with oral prednisone, at a dose

of 60 mg/d, and the lesions showed initial improvement. However, after prednisone tapering, the lesions worsened once again. Intramuscular and topical corticosteroids were administered, and the patient showed a relative clinical improvement. In agreement with the oncologist, it was decided to suspend ipilimumab. Six months after discontinuing treatment, the skin lesions had completely resolved. Administration of additional drugs was not required. In the most recent visit, the patient was asymptomatic and in follow-up with both the oncology department and the dermatology department with the aim of early detection of any tumor relapse. This involves a CT-PET scan every 3 months as well as follow-up visits every 6 months.

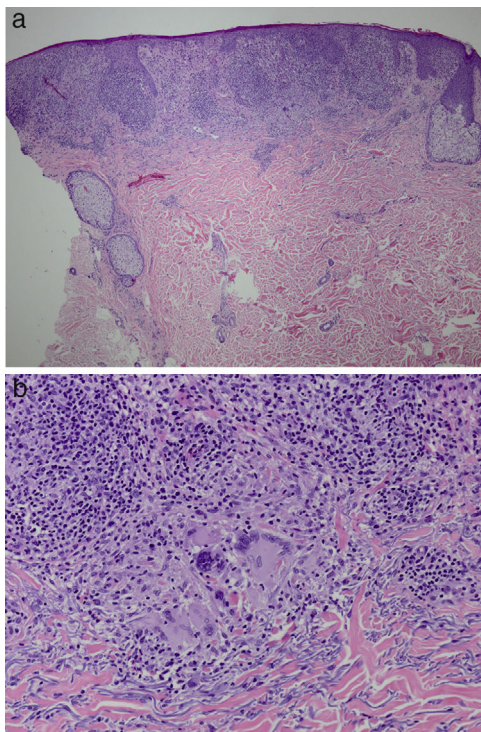
## Discussion

Granulomatous dermatoses are characterized by a predominantly dermal, reactive, non-neoplastic inflammatory infiltrate, composed principally of tissue macrophages (histiocytes), epithelioid cells, and giant multinucleated cells.<sup>1</sup> Granulomas of noninfectious etiology can be observed in granuloma annulare, annular elastolytic giant cell granuloma, necrobiosis lipoidica, interstitial granulomatous dermatitis, interstitial granulomatous drug reaction, sarcoidosis, foreign body reaction, and malignant neoplasms (for example, Sézary syndrome, Hodgkin disease, chronic B cell lymphocytic leukemia, melanoma, and other neoplasms [of lung, breast, etc]) among others.<sup>2</sup> Due to overlap of both clinical and pathological characteristics, diagnosis of this entity is often a challenge for clinicians.

Ipilimumab is a human recombinant monoclonal antibody (IgG1) that acts by inhibiting cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T lymphocyte activation, thanks to blockade of binding to B7 receptors. This leads to an increase in both activation/proliferation and production of IL-2, thereby amplifying immune response and enhancing antitumor immunity.<sup>3,4</sup> Ipilimumab was approved by the United States Food and Drug Administration (FDA) for treatment of unresectable or metastatic melanoma. The most frequent immune-related adverse drug reactions include colitis/diarrhea, dermatitis,<sup>5</sup> hepatitis, endocrinopathies, blepharitis,<sup>5</sup> transaminitis,<sup>5</sup> uveitis, hypophysitis,<sup>6</sup> nephritis,<sup>7-9</sup> thyroiditis,<sup>5</sup> and inflammatory myopathy.<sup>10-12</sup> The cutaneous adverse drug reactions observed most frequently are morbilliform rash, vitiligo, and alopecia areata.<sup>13</sup> Morbilliform rash will present mainly on the trunk and limbs. Histologically, epidermal spongiosis; edema in the papillary dermis; perivascular infiltrate composed of lymphocytes and eosinophils; and predominance of CD4 T lymphocytes in the dermis can be observed.<sup>10,11</sup> Other



**Figure 1** Clinical examination. Grouped crusty inflammatory papules distributed symmetrically on the face (A), hips (B), and ankles (C).



**Figure 2** Pathology findings. Epidermal thinning with irregular acanthosis, discrete spongiosis, and parakeratosis. The papillary dermis is replaced almost entirely by granulomas (A) and granulomatous reaction with prominent macrophages and giant cells (B). (Hematoxylin and eosin, x10.).

cutaneous adverse drug reactions which present with a lower frequency are presence of hypopigmentation, prurigo, acneiform and lichenoid rash, pyoderma gangrenosum-like ulcerations, skin toxicity in previously irradiated areas, photosensitivity reactions, and drug rash with eosinophilia and systemic symptoms (DRESS syndrome),<sup>13</sup> as well as Stevens-Johnson syndrome/toxic epidermal necrolysis.<sup>13</sup>

Sarcoidosis-like granulomatous reactions caused by ipilimumab are increasingly frequent.<sup>12</sup> Sarcoidosis is a multisystemic granulomatous entity of unknown etiology. It is usually associated with hematological neoplasms, solid tumors, and also some cancer treatments. Granuloma formation is thought to be due to an uncontrolled response of T helper 1 cells to unknown antigens. Overproduction of IL-2 and IFN- $\gamma$  may also contribute to triggering this reaction.<sup>14</sup> The absence of blockade of T cell proliferation, for example because of the effects of an anti-CTLA-4 agent, might explain the development of these granulomatous lesions, as is the case with self-reactive T cells in sarcoidosis.<sup>15</sup> The exact pathogenic mechanism by which ipilimumab induces a sarcoidosis-like granulomatous reaction is still unknown.<sup>16</sup>

The development of sarcoidosis-like granulomatous lesions, localized both in the mediastinum and lung as well as in other organs, had already been described as an adverse drug reaction<sup>5,14,16-24</sup> (Table 1). Andersen et al.<sup>19</sup> recently reported a case of a male patient who, 20 months after starting treatment with ipilimumab, presented granulomatous lesions localized only in the spleen. However, although there are several publications of sarcoidosis-like lesions induced by ipilimumab,<sup>15,16,21-23,25,-29</sup> (Table 1), exclusive involvement of the skin is considered exceptional. In addition,

**Table 1** Clinical Cases of Sarcoidosis-Like Granulomatous Reaction in Patients Diagnosed with Melanoma or Other Neoplastic Processes Treated With Ipilimumab.

Source	Sex	Age on Starting Ipilimumab	Dose of Ipilimumab, mg/kg	Neoplasm	Organ Involved			
					Skin	Lung	Mediastinal and Hilar Lymph Nodes	Others
Cervantes et al. (2017)	Male	67	10	Melanoma (stage IV)	X			
Nandavaram et al. <sup>5</sup> (2017)	Female	57	Not reported	Melanoma (stage III)			X	
Firwana et al. <sup>16</sup> (2016)	Male	41	Not reported <sup>a</sup>	Melanoma (stage III) and colon cancer (stage III)			X	Spleen and lymph nodes in the retroauricular, occipital, cervical, axillary, iliac, and inguinal regions
	Female	65	Not reported	Melanoma (stage III)	X		X	
	Female	42	Not reported <sup>b</sup>	Melanoma (stage IV)	X	X	X	Lymph nodes in the cervical, axillary, and retroperitoneal region
Reuss et al. <sup>28</sup> (2016)	Female	46	3 <sup>c</sup>	Melanoma (stage IV)	X		X	Lymph nodes in the cervical, inguinal, supraclavicular, and left iliac region
Martinez Leborans et al. <sup>29</sup> (2016)	Female	46	3	Melanoma (stage IV)	X	X		
Kim et al. <sup>21</sup> (2016)	Male	52	1 <sup>d</sup>	Urothelial carcinoma (stage IV)	X		X	Kidney
Suozzi et al. <sup>22</sup> (2016)	Female	60	1 <sup>e</sup>	Lung adenocarcinoma (stage IV)	X			
Toumeh et al. <sup>23</sup> (2016)	Female	26	3	Melanoma (stage IV)	X	X	X	Liver
Anderson et al. <sup>19</sup> (2014)	Male	55	3	Melanoma (stage IV)				Spleen
Murphy et al. <sup>20</sup> (2014)	Male	38	3	Melanoma (stage IV)			X	CNS (sella region and adjacent to the pituitary stalk)

Table 1 (Continued)

Source	Sex	Age on Starting Ipilimumab	Dose of Ipilimumab, mg/kg	Neoplasm	Organ Involved			
					Skin	Lung	Mediastinal and Hilar Lymph Nodes	Others
Tissot et al. <sup>15</sup> (2013)	Male	57	10	Melanoma (stage III)	X	X	X	
Reule and North <sup>26</sup> (2013)	Male	55	10	Melanoma (stage III)	X	X	X	
Wilgenhof et al. <sup>14</sup> (2012)	Female	56	3	Melanoma (stage IV)		X	X	Spleen, lymph nodes in the cervical and retroperitoneal region and in the base of the neck
Berthod et al. <sup>17</sup> (2012)	Male	66	3	Melanoma (stage IV)		X		
Vogel et al. <sup>18</sup> (2012)	Male	63	3	Melanoma (stage IV)			X	
van den Eertwegh et al. <sup>24</sup> (2012)	Not reported	Not reported	5 <sup>f</sup>	Castration-resistant prostate cancer (stage IV)		X		
Eckert et al. <sup>25</sup> (2009)	Female	71	10	Melanoma (stage IV)	X	X	X	
Seve et al. <sup>27</sup> (2009)	Female	67	Not reported	Melanoma (stage IV)	X		X	Bronchial epithelium

<sup>a</sup> Patient treated with adjuvant mFOLFOX6 and ipilimumab.

<sup>b</sup> Patient treated initially with ipilimumab and vemurafenib, with subsequent switch to pembrolizumab. Swollen lymph nodes presented after receiving treatment with pembrolizumab.

<sup>c</sup> Patient treated with ipilimumab (3 mg/kg)/nivolumab(1 mg/kg) in combined infusions.

<sup>d</sup> Patient treated with ipilimumab (1 mg/kg)/nivolumab(3 mg/kg) in combined infusions.

<sup>e</sup> Patient treated with ipilimumab (1 mg/kg)/nivolumab(1 mg/kg) in combined infusions.

<sup>f</sup> Patient treated with ipilimumab (5 mg/kg)/granulocyte-macrophage colony stimulating factor-transduced allogeneic prostate cancer cells vaccine (GVAX) in combined infusions.



unlike other cases, in which the granulomatous reaction presents in the first weeks or months, in our patient, presentation occurred 18 months after initiation of ipilimumab, in the form of a diffuse cutaneous granulomatous reaction. Clinical improvement was only achieved after suspension of ipilimumab.

In summary, this case can be considered both a diagnostic and therapeutic challenge, as clinically, the patient was refractory to high doses of corticosteroids and his condition only improved after suspending ipilimumab. We also highlight the importance of close follow-up of patients treated with ipilimumab as there has been shown to be a risk of developing sarcoidosis-like granulomatous lesions as an adverse drug reaction. To the best of our knowledge, this is the first case described in a patient diagnosed with melanoma who presented a granulomatous reaction confined to the skin as a side effect of ipilimumab.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Acknowledgments

We thank the patient for authorizing the publication of this case. Likewise, we thank Dr. George W. Elgart, of the Dermatology and Cutaneous Surgery Department, Faculty of Medicine of the Miller University in Miami, United States, who supported us with pathology images and Dr. Sadegh Amini of the Dermatology and Cutaneous Surgery Department, Faculty of Medicine of the Miller University in Miami, United States, who helped us with this case. Those acknowledged did not receive any recompense.

## References

- Rabinowitz LO, Zaim MT. A clinicopathologic approach to granulomatous dermatoses. *J Am Acad Dermatol.* 1996;35:588–600.
- Fischer M, Wohlrab J, Audring TH, Sterry W, Marsch WC. Granulomatous mycosis fungoides Report of two cases and review of the literature. *J Eur Acad Dermatol Venereol.* 2000;14:196–202.
- Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363:711–23.
- Culver ME, Gatesman ML, Mancl EE, Lowe DK. Ipilimumab: a novel treatment for metastatic melanoma. *Ann Pharmacother.* 2011;45:510–9.
- Nandavaram S, Nadkarni A. Ipilimumab-induced sarcoidosis and thyroiditis. *Am J Ther.* 2017.
- Lam T, Chan MM, Sweeting AN, De Sousa SM, Clements A, Carlino MS, et al. Ipilimumab-induced hypophysitis in melanoma patients: an Australian case series. *Intern Med J.* 2015;45:1066–73.
- Thajudeen B, Madhrira M, Bracamonte E, Cranmer LD. Ipilimumab granulomatous interstitial nephritis. *Am J. Ther.* 2015;22:e84–7.
- Izzedine H, Gueutin V, Gharbi C, Mateus C, Robert C, Routier E, et al. Kidney injuries related to ipilimumab. *Invest New Drugs.* 2014;32:769–73.
- Belliere J, Meyer N, Mazieres J, Ollier S, Boulinguez S, Delas A, et al. Acute interstitial nephritis related to immune checkpoint inhibitors. *Br J Cancer.* 2016;115:1457–61.
- Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Semin Oncol.* 2010;37:499–507.
- Collins LK, Chapman MS, Carter JB, Samie FH. Cutaneous adverse effects of the immune checkpoint inhibitors. *Curr Probl Cancer.* 2016.
- Abdel-Wahab N, Shah M, Suarez-Almazor ME. Adverse events associated with immune checkpoint blockade in patients with cancer: A systematic review of case reports. *PLoS One.* 2016;11:e0160221.
- Voskens CJ, Goldinger SM, Loquai C, Robert C, Kaehler KC, Berking C, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLoS One.* 2013;8:e53745.
- Wilgenhof S, Morlion V, Seghers AC, Du Four S, Vanderlinden E, Hanon S, et al. Sarcoidosis in a patient with metastatic melanoma sequentially treated with anti-CTLA-4 monoclonal antibody and selective BRAF inhibitor. *Anticancer Res.* 2012;32:1355–9.
- Tissot C, Carsin A, Freymond N, Pacheco Y, Devouassoux G. Sarcoidosis complicating anti-cytotoxic T-lymphocyte-associated antigen-4 monoclonal antibody biotherapy. *Eur Respir J.* 2013;41:246–7.
- Firwana B, Ravilla R, Raval M, Hutchins L, Mahmoud F. Sarcoidosis-like syndrome and lymphadenopathy due to checkpoint inhibitors. *J Oncol Pharm Pract.* 2016.
- Berthod G, Lazor R, Letovanec I, Romano E, Noirez L, Mazza Stalder J, et al. Pulmonary sarcoid-like granulomatosis induced by ipilimumab. *J Clin Oncol.* 2012;30:e156–9.
- Vogel WV, Guislain A, Kvistborg P, Schumacher TN, Haanen JB, Blank CU. Ipilimumab-induced sarcoidosis in a patient with metastatic melanoma undergoing complete remission. *J Clin Oncol.* 2012;30:e7–10.
- Andersen R, Norgaard P, Al-Jailawi MK, Svane IM. Late development of splenic sarcoidosis-like lesions in a patient with metastatic melanoma and long-lasting clinical response to ipilimumab. *Oncoimmunology.* 2014;3:e06–9545.
- Murphy KP, Kennedy MP, Barry JE, O'Regan KN, Power DG. New-onset mediastinal and central nervous system sarcoidosis in a patient with metastatic melanoma undergoing CTLA4 monoclonal antibody treatment. *Oncol Res Treat.* 2014;37:351–3.
- Kim C, Gao J, Shannon VR, Siefker-Radtke A. Systemic sarcoidosis first manifesting in a tattoo in the setting of immune checkpoint inhibition. *BMJ Case Rep.* 2016;2016.
- Suoizzi KC, Stahl M, Ko CJ, Chiang A, Gettinger SN, Siegel MD, et al. Immune-related sarcoidosis observed in combination ipilimumab and nivolumab therapy. *JAAD Case Rep.* 2016;2:264–8.
- Toume A, Sakhi R, Shah S, Arudra SK, de Las Casas LE, Skeel RT. Ipilimumab-induced granulomatous disease occurring simultaneously with disease progression in a patient with metastatic melanoma. *Am J Ther.* 2016;23:e1068–71.
- van den Eertwegh AJ, Versluis J, van den Berg HP, Santegoets SJ, van Moorselaar RJ, van der Sluis TM, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol.* 2012;13:509–17.
- Eckert A, Schoeffler A, Dalle S, Phan A, Kiakouama L, Thomas L. Anti-CTLA4 monoclonal antibody induced sarcoidosis in a metastatic melanoma patient. *Dermatology.* 2009;218:69–70.

26. Reule RB, North JP. Cutaneous and pulmonary sarcoidosis-like reaction associated with ipilimumab. *J Am Acad Dermatol*. 2013;69:e272-3.
27. Seve P, Schott AM, Pavic M, Broussolle C, Gilis L, Thomas L. Sarcoidosis and melanoma: a referral center study of 1,199 cases. *Dermatology*. 2009;219:25-31.
28. Reuss JE, Kunk PR, Stowman AM, Gru AA, Slingluff CL Jr, Gaughan EM. Sarcoidosis in the setting of combination ipilimumab and nivolumab immunotherapy: a case report & review of the literature. *J Immunother Cancer*. 2016;4:94.
29. Martinez Leborans L, Esteve Martinez A, Victoria Martinez AM, Alegre de Miquel V, Berrocal Jaime A. Cutaneous sarcoidosis in a melanoma patient under Ipilimumab therapy. *Dermatol Ther*. 2016;29:306-8.