

The value of histopathological diagnosis in the elderly patients with granulomatous dermatoses. Case series

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Abstract

Granulomatous inflammations are a particular type of chronic septic or aseptic inflammation, in which infectious or non-infectious agents are difficult to eliminate by the immune system. These are type IV hypersensitivity reactions mediated by pre-sensitized T-lymphocytes cells CD4+ and CD8+ lymphocytes. Disorders included in this category are: tuberculosis, leprosy, syphilis, sarcoidosis, type I diabetes, multiple sclerosis, Crohn's disease and rheumatoid arthritis. At cutaneous level, this pattern of granulomatous reaction is characterized by a chronic inflammation with formation of granulomas consisting of a variable number of histiocytes, multinucleated giant cells and lymphocytes. Granulomatous dermatoses should be differentiated from other primary or secondary lesions affecting the skin such as inflammation or tumors. Often granulomatous dermatoses can be confused with other skin disorders, both clinically and histological. Histopathology examination can add important information and clarify the diagnosis. This paper presents a series of three clinical cases of granulomatous skin occurring in the elderly patients confirmed at histology examination. Clinical and histology criteria were analyzed, along with specific differential diagnosis, based on data from the literature.

Keywords: granulomatous dermatoses, elderly patients, histopathological examination.

Introduction

Granulomatous inflammations are a particular type of chronic septic or aseptic inflammation, in which infectious and non-infectious agents are difficult to eliminate by the immune system. These are type IV hypersensitivity reactions mediated by pre-sensitized T-lymphocytes cells CD4+ and CD8+ lymphocytes. Disorders included in this category are: tuberculosis, leprosy, syphilis, sarcoidosis, type I diabetes, multiple sclerosis, Crohn's disease and rheumatoid arthritis. This type of mechanism is also present in the phenomenon of acute cellular rejection of solid organs: heart, liver, kidneys [1, 2]. At cutaneous level, the pattern of granulomatous reaction is characterized by the presence of chronic inflammation with formation of granulomas consisting of a variable number of histiocytes, multinucleated giant cells and lymphocytes. Skin lesions can be subgrouped according to the architecture of granulomas, their location, the presence or absence of central necrosis and the presence or absence of foreign material body [3].

Antigens presenting cells (APCs) are involved in granuloma development, which by means of interleukin 12 (IL-12) or directly by activating CD4+ lymphocytes produce a number of pro-inflammatory cytokines: IL-2, tumor necrosis factor (TNF)- α , TNF- γ . Proinflammatory factors act on circulating monocytes, which in tissues and cells turns into histiocytes and multinucleated giant cells. Profibrogenic factors activate the fibroblasts with

synthesis of collagen fibers and together with the lymphocyte type, inflammatory cells lead to the appearance of granuloma [1, 4].

From a clinical point of view, the cutaneous aspects are often intricate and difficult to categorize etiologically and therapeutically. In many cases, a skin biopsy with histopathological examination is needed to establish a diagnosis of certainty. Most of these disorders are systemic and usually the skin is secondary involved. There are also disorders with the skin as the primary involved organ. The appearance of these granulomatous skin disorders in elderly may be due to photo aging, skin trauma, visceral neoplasms or various drugs [5].

Granulomatous dermatoses should be differentiated from other primary or secondary skin lesions of an inflammatory or tumoral nature. Often granulomatous dermatoses can be difficult to differentiate both clinically and histologically. The histopathology examination completes and clarifies the diagnosis.

This paper presents a series of three clinical cases of cutaneous granulomatous disorders occurring in the elderly patients that were confirmed with histopathology. Clinical and histopathological criteria were analyzed, along with the specific differential diagnosis, based on data from the literature [6, 7].

Patients, Materials and Methods

Our study presents a series of three cases with cutaneous

granulomatous pathology from the Clinic of Dermatology, Tîrgu Mureş. As a particular fact, the age of these patients is between 61 and 78 years. All patients were examined clinically and paraclinical (dermatoscopy, abdominal-pelvic ultrasound, radiology, hematology). Excisional biopsy was performed with 2% lidocaine as a local anesthetic. Tissue fragments were processed according to the standard histological methods: 4% formalin fixation, paraffin embedding, sectioning, staining with Hematoxylin and Eosin (HE), trichromic van Gieson (VG), and Periodic Acid-Schiff (PAS).

Case presentations

Case No. 1

A 78-year-old male patient with a personal history of chronic professional sun exposure came to the Clinic of Dermatology for the emergence on the trunk and limbs of disseminated erythematous plaques and patches with an annular aspect, an infiltrated peripheral zone and pale center. The lesions were asymptomatic and started two months ago on the posterior thorax and expanded progressively. The clinical suspicion was that of cutaneous sarcoidosis or annular granuloma. A skin biopsy from the edge of one of the lesions was performed and the histology showed the presence of palisaded granulomas with central necrobiosis. Based on histology findings and correlated with the clinical aspect a diagnosis of annular granuloma was established. Due to the advanced age and some digestive complaints associated with episodes of abdominal pain and constipation, some investigations for the detection of possible neoplastic or non-neoplastic visceral disorders were conducted. The computed tomography (CT) scan of the thorax and abdomen, the upper gastrointestinal endoscopy and colonoscopy revealed no visceral injuries. The glycemia was within normal limits, with no signs of type II diabetes mellitus. The ELISA serology for *Borrelia burgdorferi* (IgM, IgG antibodies) was negative. At discharge, the patient was advised to avoid sun exposure. The evolution of the lesions was favorable with topical corticosteroid therapy (0.1% mometasone furoate bid) (Figure 1).

Case No. 2

A 61-year-old male patient known with gout for over six years, with a poorly therapeutic control due to a low compliance, presented for a dermatological consult for the occurrence of small-indurated papular lesions with a whitish “milia-like” appearance on the palmar areas of the hands. At the time of admission, the laboratory results showed: serum uric acid 8.6 mg/dL (normal values 3 to 7.2 mg/dL), serum creatinine 2.3 mg/dL (normal values 0.5–1.2 mg/dL), inflammatory biological syndrome – erythrocyte sedimentation rate (ESR) 40 mm/h (normal values 3–20 mm/1 h), fibrinogen 520 mg/dL (normal values 180–350 mg/dL), C-reactive protein 2 mg/dL (normal values 0–0.9 mg/dL). The histopathology revealed the presence in the dermis of numerous deposits of uric acid accompanied by fibrosis, cell debris, lymphocyte infiltration and numerous foreign body type giant cells. Based on this aspect the diagnosis was that of chronic tophaceous gout. The patient had also other associated chronic

diseases such as: stage II arterial hypertension, chronic renal failure, liver cirrhosis consequent to a chronic viral type C hepatitis and grade II obesity (Figure 2).

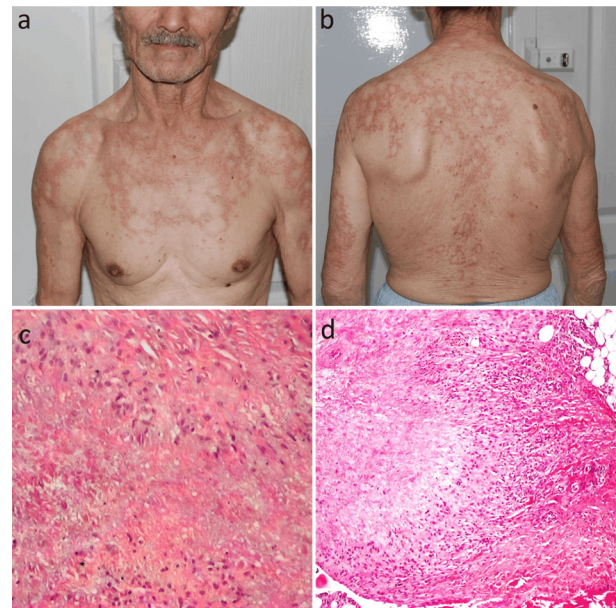


Figure 1 – (a and b) Granuloma annulare. Clinical aspects; (c and d) Palisading granulomas with central necrobiosis.

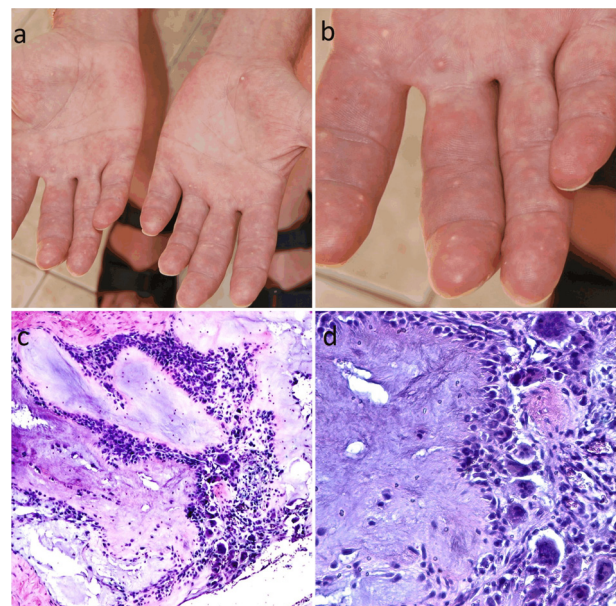


Figure 2 – (a and b) Chronic tophaceous gout – clinical aspects; (c and d) Presence of numerous deposits in dermis of uric acid accompanied by fibrosis, cell debris, lymphocyte infiltration and numerous giant cells as foreign bodies.

Case No. 3

A 71-year-old female patient presented to a dermatological consult for the presence of about 10 years on the face, anterior cervical region and the right arm of well defined, infiltrated erythematous plaques with sizes between 2/2 cm and 4/4 cm. The lesions were asymptomatic. On the vitropression of the lesions with a glass slide (diascopy), an “apple jelly” look was seen. The clinical suspicion was that of cutaneous sarcoidosis or skin tuberculosis (lupus vulgaris with multiple lesions). A skin biopsy was

performed and the histology revealed the presence of numerous granulomas with no central necrosis, multinucleated giant cells and the presence of asteroid bodies. A chest radiograph was performed followed by a pneumology consult to exclude tuberculosis. The CT examination showed no evidence of sarcoidosis or tuberculosis lesions in other organs. The level of angiotensin converting enzyme was 35 U/L (normal values 12–68 U/L). The patient received treatment with topical superpotent corticosteroid (clobetasol propionate ointment 0.5 mg/g) with a stationary evolution of lesions after 30 days of treatment. Minocycline treatment was initiated 100 mg/day with a favorable evolution of the lesions. Currently, the patient has regular clinical and paraclinical follow-ups in our Clinic (Figures 3–5).

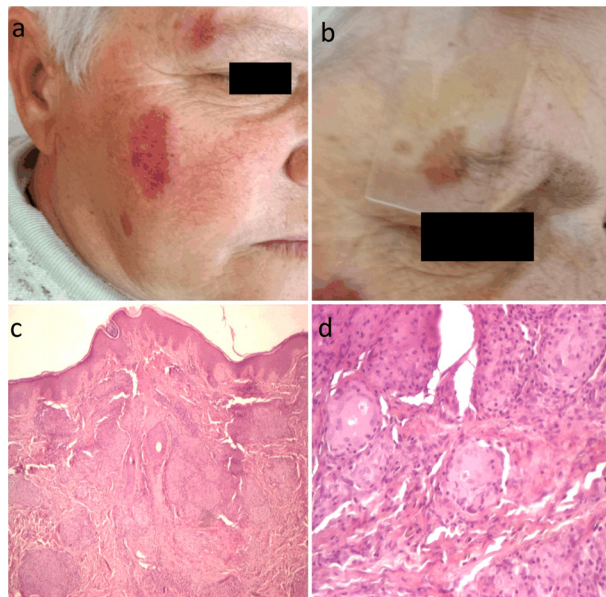


Figure 3 – (a) Erythematous plaques on the face; (b) Diascopy – “apple jelly” aspect; (c and d) Typical granuloma of sarcoidosis, without central necrosis, with giant multinucleated cells and asteroid bodies.

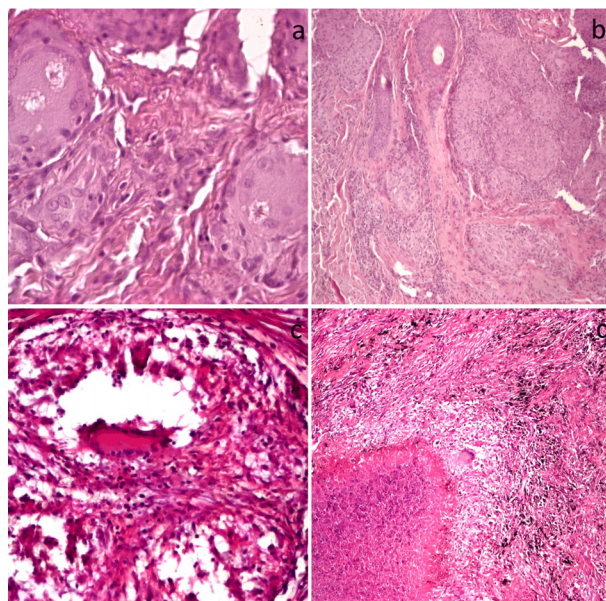


Figure 4 – Differential diagnosis of granulomatous diseases: (a and b) Foreign body granuloma to suture material; (c and d) Granuloma annulare – palisading granulomas with no central necrosis.

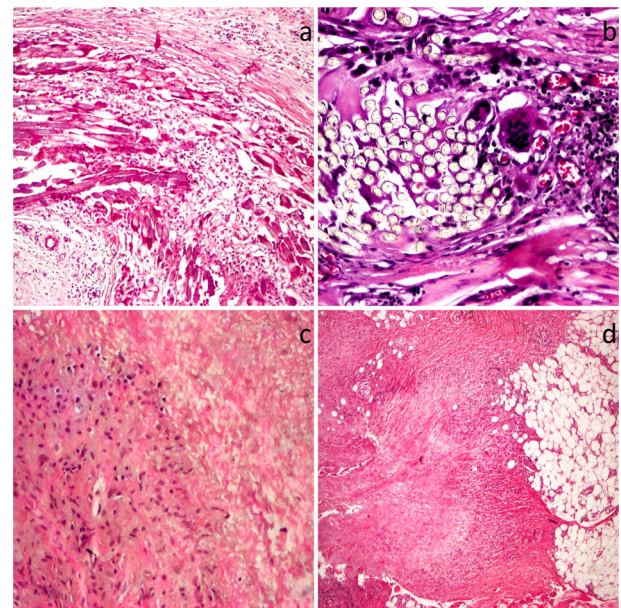


Figure 5 – Differential diagnosis of granulomatous diseases: (a and b) Cutaneous sarcoidosis – granulomas with no central necrosis, giant multinucleated cells, asteroid bodies; (c) Pulmonary tuberculosis – Langhans cell; (d) Pulmonary tuberculosis – Koster nodule, caseous necrosis.

Discussion

The etiology of granulomatous dermatoses often remains unidentified (sarcoidosis, granuloma annulare), but there are also some obvious causes for these disorders (tuberculosis, leprosy, gout, foreign body granuloma).

The pathophysiological mechanisms involve the type IV hypersensitivity reactions, the tuberculid or the delayed type. The prototype for these disorders is tuberculosis or leprosy, but in the same category, there is also sarcoidosis, granuloma annulare, syphilis, foreign body granulomas [1, 8].

The clinical aspects are often overlapping, the histology examination being the one to determine an accurate diagnosis, thus imposing the appropriate treatment. The differential diagnosis includes inflammatory lesions, infections and tumoral lesions. The microscopic diagnosis of skin granulomas involves a detailed differential diagnosis that should exclude or include a series of histopathological parameters. Although there is no globally agreed single classification, the lesions can fit into a certain tissue pattern [9].

The tuberculid type granulomas include skin tuberculosis, tuberculids, leprosy, advanced stage cutaneous syphilis, perioral dermatitis and Crohn's disease. It is characterized by the presence of Langhans cells with nuclei in a “crown” or “horseshoe” disposition with the presence of caseous necrosis in the center of the nodules. Skin tuberculosis is often accompanied by visceral localizations and responds favorably to treatment with tuberculostatics [10].

The sarcoidotic type granuloma includes skin sarcoidosis, foreign body granulomas (silica, silicon and beryllium), secondary syphilis, and some lymphoproliferative syndromes (Sezary syndrome or non-Hodgkin's lymphoma with cutaneous manifestations). It is characterized by small or medium-sized, round or oval granulomas with no central caseous necrosis (naked granulomas). The multinucleated giant cells may contain inclusions that are not specific to

sarcoidosis, but may bring an additional histopathological clue: Schaumann bodies and asteroid bodies. Schaumann bodies are basophilic structures, round, composed of calcium carbonate, calcium phosphate and iron oxalate. Asteroid bodies are eosinophilic cytoplasmic structures with a star shape appearance [11, 12]. Granulomas with central necrobiosis or collagenolysis are present in disorders like granuloma annulare, necrobiosis lipoidica or rheumatoid nodules. The collagen fibers necrobiosis from the center of the granuloma is surrounded by a lymphocytic and histiocytic inflammatory infiltrate typically arranged as a peripheral palisade. In the center, lesions may be basophile due to acid mucopolysaccharides or may be eosinophilic due to foci of fibrosis [13, 14].

Foreign body granulomas appear around the foreign body structures: surgical sutures, fragments of glass, wood, metal, etc. The foreign body is often identified along with a variable number of characteristic multinucleated giant cells and also inflammatory cells: lymphocytes, histiocytes, neutrophils. The foreign body can have endogenous origin (keratin from a ruptured epidermoid cysts, hair, calcium deposits, oxalates or uric acid from tophi). These granulomas often can get a superimposed infection and can lead to suppurative granulomas with localized or regionalized lesions [15].

One can also find xanthogranulomatous type granulomas or granulomas with uncharacteristic aspects. This category includes the juvenile xanthogranuloma with histiocytes that phagocytose the lipids and turn into foam cells and chalazion that develops due to the lipid material from the sebaceous glands of the eyelids [16].

Granulomatous dermatoses are cited in the literature as cutaneous reactions to various exogenous or endogenous factors. One of the external factors involved is skin trauma, e.g., insect bites, dermatological-cosmetic procedures or tattoos [17].

The appearance of lesions on the skin areas previously affected by various dermatoses is called a Wolf isotopic response. Jaka-Moreno *et al.* found that the granulomatous dermatoses are the main lesions occurring in the context of Wolf phenomenon. They describe the occurrence of granulomatous dermatoses in four out of nine patients on the previously affected by herpes zoster dermatomes [18].

In some cases, an association was found with rheumatologic diseases such as rheumatoid arthritis and ankylosing spondylitis [19, 20].

The occurrence of granulomatous skin lesions with no infectious or tumoral etiology may signal the presence of neoplastic, especially hematological processes [21, 22]. It was also reported to be associated with lung and esophageal cancer [23, 24].

On the other hand, cutaneous metastases of visceral malignancies may appear clinical and histological as granulomatous dermatoses such as interstitial granulomatous dermatitis or granuloma annulare. Hartman *et al.* [25] describe three cases in which the immunohistochemical analysis revealed tumoral cells and also their source. Thus, granulomatous skin lesions occurring in elderly patients with a history of cancer or with clinical signs of internal organs involvement require a careful pathological and immunohistochemical assessment of these skin lesions.

Certain drugs are involved in causing granulomatous dermatoses. The most commonly cited granulomatous

dermatoses occurrences are in the context of the patients with psoriasis or rheumatoid arthritis treated with anti-TNF- α agents. The reported biological agents are etanercept and adalimumab [26, 27].

The histopathological diagnosis of granulomatous dermatoses requires an interdisciplinary approach with the dermatologist, the pathologist and the internal medicine physician in order to identify the determining factor. Granulomatous dermatoses require laboratory investigations to detect a possible malignancy or the extension of these lesions in other organs as in cutaneous sarcoidosis. The chronic medication should be carefully considered as well as the history of skin injuries including any preexisting dermatitis in the affected skin regions. The detection and elimination of such causes can lead to remission in most cases. In older patients, the appearance of granulomatous dermatoses should impose a thorough evaluation in order to identify the visceral malignancies as well as a careful assessment of the medication considering that these patients usually follow a chronic drug therapy [28].

If a cause cannot be identified for the cutaneous granulomatoses, the therapeutic options can have a debatable efficiency. Granuloma annulare can benefit from local corticosteroid therapy, or rarely from systemic corticotherapy. Phototherapy can also be used with a beneficial effect in most cases [29].

Phototherapy requires caution because granuloma annulare lesions can be triggered by ultraviolet radiation in older people with photo aged skin [30]. We consider the case of our patient as being possibly caused by a chronic exposure to ultraviolet radiation due to chronic professional sun exposure, but also because of the favorable evolution of the skin lesions following the avoidance of sun exposure. We also considered noteworthy the regressive character of the granuloma annulare lesions after local injury, *i.e.*, after skin biopsy [31].

Cutaneous sarcoidosis, with no involvement of other organs, is treated with topical corticosteroids. There have been published reports of rapid resolution of the lesions following treatment with systemic tetracycline and minocycline [32]. The case our patient had some particularities such as: unaffected internal organs and localization across several skin regions.

Tophi usually characterize the advanced stages of gout. The appearance of this type of lesion requires the lowering of the serum uric acid levels and the prevention of uric acid crystals formation with treatments such as allopurinol, colchicine, probenecid. Our patient developed tophi mostly due to the long evolution of the disease and the inefficient therapeutic control due to the low compliance. Considering the reported cases of angiosarcoma and fibrosarcoma that developed on tophi, we consider that periodic dermatological evaluation is absolutely necessary [33].

✦ Conclusions

Granulomatous dermatoses require histopathological examination for a diagnosis of certainty as well as for including them in clinical context. The appearance of these granulomatous skins disorders in elderly may have multiple causes such as chronic sun exposure and skin trauma, and require laboratory investigations to rule out the involvement of other organs or to detect visceral neoplastic processes.

Conflict of interests

The authors declare that they have no conflict of interests.

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References

- [1] Vartolomei MD, Cotoi OS, Badea MA, Chibelea CB, Cotoi T, Morariu V, Albu C, Morariu SH. Indurative edema of the prepuce mimicing phimosi, an atypical manifestation of primary syphilis. *Acta Dermatovenereol Croat*, 2015, 23(4):301–303.
- [2] James DG. A clinicopathological classification of granulomatous disorders. *Postgrad Med J*, 2000, 76(898):457–465.
- [3] Roxo-Junior P, Simão HM. Chronic granulomatous disease: why an inflammatory disease? *Braz J Med Biol Res*, 2014, 47(11):924–928.
- [4] Zissel G. Cellular activation in the immune response of sarcoidosis. *Semin Respir Crit Care Med*, 2014, 35(3):307–315.
- [5] Badea MA, Morariu SH, Sin A. A novel disease caused by increase of the lifespan: chronic cutaneous insufficiency syndrome or dermatoporosis. *Acta Med Marisiensis*, 2015, 61(1):54–56.
- [6] Hawryluk EB, Izikson L, English JC 3rd. Non-infectious granulomatous diseases of the skin and their associated systemic diseases: an evidence-based update to important clinical questions. *Am J Clin Dermatol*, 2010, 11(3):171–181.
- [7] Szabo B, Crișan D, Tompa I, Szabo I. Isolated neurosarcoidosis. *Rom J Morphol Embryol*, 2011, 52(3 Suppl):1139–1142.
- [8] Rieder E, Desai S, Mundi JP, Boyd KP, Patel RR, Ramachandran S, Franks AG Jr. Granulomatous dermatitis related to silicone implant. *Dermatol Online J*, 2013, 19(12):20708.
- [9] Ricketts JR, Rothe MJ, Grant-Kels JM. Cutaneous simulants of infectious disease. *Int J Dermatol*, 2011, 50(9):1043–1057.
- [10] Hackett CB, Maguire A, Heffernan E, Sheahan K, Collins P. An unusual cause of granulomatous dermatitis and panniculitis. *Clin Exp Dermatol*, 2012, 37(1):81–83.
- [11] Lo Schiavo A, Ruocco E, Gambardella A, O’Leary RE, Gee S. Granulomatous dysimmune reactions (sarcoidosis, granuloma annulare, and others) on differently injured skin areas. *Clin Dermatol*, 2014, 32(5):646–653.
- [12] Mahony J, Helms SE, Brodell RT. The sarcoidal granuloma: a unifying hypothesis for an enigmatic response. *Clin Dermatol*, 2014, 32(5):654–659.
- [13] Wood A, Hamilton SA, Wallace WA, Biswas A. Necrobiotic granulomatous tattoo reaction: report of an unusual case showing features of both necrobiosis lipidica and granuloma annulare patterns. *Am J Dermatopathol*, 2014, 36(8):e152–e155.
- [14] Pătrașcu V, Giurcă C, Ciurea RN, Georgescu CC, Ciurea ME. Ulcerated necrobiosis lipidica to a teenager with diabetes mellitus and obesity. *Rom J Morphol Embryol*, 2014, 55(1):171–176.
- [15] Joyce S, Rao Sripathi BH, Mampilly MO, Firdoose Nyer CS. Foreign body granuloma. *J Maxillofac Oral Surg*, 2014, 13(3):351–354.
- [16] Szalat R, Pirault J, Femand JP, Carrié A, Saint-Charles F, Olivier M, Robillard P, Frisdal E, Villard EF, Cathébras P, Bruckert E, Chapman MJ, Giral P, Guerin M, Lesnik P, Le Goff W. Physiopathology of necrobiotic xanthogranuloma with monoclonal gammopathy. *J Intern Med*, 2014, 276(3):269–284.
- [17] Soltani-Arabshahi R, Wong JW, Duffy KL, Powell DL. Facial allergic granulomatous reaction and systemic hypersensitivity associated with microneedle therapy for skin rejuvenation. *JAMA Dermatol*, 2014, 150(1):68–72.
- [18] Jaka-Moreno A, López-Pestaña A, López-Núñez M, Ormaechea-Pérez N, Vildosola-Esturo S, Tuneu-Valls A, Lobo-Morán C. Wolf’s isotopic response: a series of 9 cases. *Actas Dermosifiliogr*, 2012, 103(9):798–805.
- [19] Stephenson SR, Campbell SM, Drew GS, Magro CM. Palisaded neutrophilic and granulomatous dermatitis presenting in a patient with rheumatoid arthritis on adalimumab. *J Cutan Pathol*, 2011, 38(8):644–648.
- [20] de Unamuno Bustos B, Rabasco AG, Sánchez RB, de Miquel VA. Palisaded neutrophilic and granulomatous dermatitis associated with ankylosing spondylitis. *Am J Dermatopathol*, 2013, 35(8):847–850.
- [21] Hagiwara A, Fujimura T, Furudate S, Kambayashi Y, Numata Y, Haga T, Aiba S. Generalized granulomatous dermatitis accompanied by myelodysplastic syndrome. *Acta Derm Venereol*, 2014, 94(2):223–224.
- [22] Cornejo KM, Lum CA, Izumi AK. A cutaneous interstitial granulomatous dermatitis-like eruption arising in myelodysplasia with leukemic progression. *Am J Dermatopathol*, 2013, 35(2):e26–e29.
- [23] Moyano Almagro B, López Navarro N, Contreras Steyls M, Gallego Dominguez E, Herrera Acosta E, Herrera Ceballos E. Interstitial granulomatous dermatitis and arthritis revealing oesophageal carcinoma. *Clin Exp Dermatol*, 2013, 38(5):501–503.
- [24] Schreckenber C, Asch PH, Sibilia J, Walter S, Lipsker D, Heid E, Grosshans E. Interstitial granulomatous dermatitis and paraneoplastic rheumatoid polyarthritis disclosing cancer of the lung. *Ann Dermatol Venereol*, 1998, 125(9):585–588.
- [25] Hartman RI, Chu EY, Acker SM, James WD, Elenitsas R, Kovarik CL. Cutaneous metastases from visceral malignancies mimicking interstitial granulomatous processes: a report of 3 cases. *Am J Dermatopathol*, 2013, 35(5):601–605.
- [26] Samimi M, Lorette G, Machet L, de Muret A, Watier H, Maruani A. Facial granulomatous nodules during etanercept treatment for psoriasis. *Int J Dermatol*, 2009, 48(9):1025–1027.
- [27] Umezawa Y, Ito K, Nakagawa H. Palisaded neutrophilic and granulomatous dermatitis in a rheumatoid arthritis patient after treatment with adalimumab. *Eur J Dermatol*, 2013, 23(6):910–911.
- [28] Aung PP, Bowker B, Masterpol KS, Mahalingam M. Disseminated noninterstitial granulomatous dermatitis as a cutaneous manifestation of the preleukemic state in a patient with myelodysplasia and ulcerative colitis – apropos a case and review of the literature. *Am J Dermatopathol*, 2014, 36(7):e117–e120.
- [29] Simon JC, Pfieger D, Schöpf E. Recent advances in phototherapy. *Eur J Dermatol*, 2000, 10(8):642–645.
- [30] Regan W. Actinic radiation plays a significant role in the etiology of actinic granuloma lesions. *Int J Dermatol*, 2006, 45(8):1001.
- [31] Levin NA, Patterson JW, Yao LL, Wilson BB. Resolution of patch-type granuloma annulare lesions after biopsy. *J Am Acad Dermatol*, 2002, 46(3):426–429.
- [32] Sheu J, Saavedra AP, Mostaghimi A. Rapid response of tattoo-associated cutaneous sarcoidosis to minocycline: case report and review of the literature. *Dermatol Online J*, 2014, 20(8).
- [33] Wang JJ, Wang HY, Cheng K, Wang X, Yu B, Shi SS, Zhou XJ, Shi QL. Fibrosarcoma arising from gouty tophi: report of a unique case and review of literature. *Int J Clin Exp Pathol*, 2015, 8(4):4227–4232.

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