REVIEW

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The inflammatory infiltrate of melanocytic nevus

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Abstract

Melanocytic nevi are frequently accompanied by inflammatory cells of different types, in varied amounts and distributed in different patterns. In the current report, we review the knowledge on inflammation seen in different types of melanocytic nevi. As an additional contribution, we studied the lymphocytic inflammatory component of Duperrat nevus, as well as the cytotoxic component of Sutton nevus, two contributions that we have not found in the literature. We conclude that: (*a*) Duperrat nevus has a mixed inflammatory reaction that includes histiocytes, foreign-body multinucleated giant cells, polymorphonuclears, lymphocytes (predominantly CD4+) and plasma cells (commonly abundant); (*b*) common melanocytic nevi with reactive inflammatory infiltrate usually show a CD4+ predominant population; (*c*) Meyerson nevus commonly shows an inflammatory infiltrate mainly made up of CD4+ T-cells; (*d*) Sutton nevus with halo phenomenon is accompanied by a dense inflammatory infiltrate with lymphocytes in a CD4:CD8 ratio varying from 1:1 to 1:3 and in which most of the CD8+ T-cells do not express cytotoxic markers; (*e*) Wiesner nevus commonly shows a spare lymphocytic infiltrate but the nature of the infiltrate has not yet been investigated.

Keywords: Duperrat nevus, Meyerson nevus, Wiesner nevus, Sutton nevus, regression.

Introduction

Melanocytic nevi are frequently accompanied by inflammatory cells of different types, in varied amounts and distributed in different patterns. This inflammatory component provides additional information about the melanocytic lesion. For instance, a certain degree of atypia (otherwise worrying if seen out of context) can be ignored in an inflamed nevus. Some inflammatory cells (for instance, plasma cells) can favor a diagnosis of melanocytic malignancy in the appropriate context.

The nature of the chronic lymphocytic inflammatory infiltrate of some types of nevi has not been studied previously: in some cases, this was due to the recent description of the nevus type (such as Wiesner nevus); in others, it was probably due to the overwhelming additional non-lymphocytic inflammatory components (such as in Duperrat nevus).

In the current report, we review the knowledge on inflammation seen in different types of melanocytic nevi.

Duperrat nevus: inflammation not directly related to the nevus

Duperrat nevus shows inflammation caused by the rupture of a folliculo-sebaceous unit or of an epidermal cyst [1]. The inflammatory infiltrate is usually granulomatous, with giant cell response of foreign-body type, many times surrounding keratin. Polymorphonuclears are also notorious, even within areas of abscessification. In some Duperrat nevi, there is also a lymphocytic infiltrate. The nature of these lymphocytes has not been previously investigated in the literature, to the best of our knowledge.

We have studied the expression of CD4 and CD8 by the lymphocytic infiltrate in eight cases of Duperrat nevi. Table 1 shows the age, gender and nevus location of the cases, as well as the CD4:CD8 ratio in each case.

Table 1 – *Studied cases of Duperrat nevus*

Case No.	Age [years]	Gender	Location of the lesion	CD4/CD8 ratio [%]	CD138: maximum number per high power field (400×)
1.	61	F	Eyebrow	60/40	239
2.	66	F	Unknown	80/20	33
3.	14	M	Chin	90/10	265
4.	39	F	Unknown	90/10	364
5.	30	M	Back	80/20	1
6.	23	M	Forehead	60/40	2
7.	28	F	Cheek	85/15	164
8.	52	F	Cheek	70/30	695

F: Female; M: Male.

All cases showed marked predominance of CD4+ T-cells (Figure 1) and in five of them, CD4+ cells represented more than 80% of the T-cells (Table 1). We also immunostained all cases for CD138 and quantified the maximum number of plasma cells evidenced in one high-power field (HPF) (400×) (Table 1). To our surprise, plasma cells were neither an oddity nor scarce; to the contrary, most cases were rich in plasma cells, with up to 695 in one HPF (Case No. 8).

Melanocytic nevus with reactive non-specific inflammatory infiltrate

Chronic inflammatory infiltrate accompanying melanocytic nevi is not uncommon, and the cause of the infiltrate is not always clear. Exogenic irritation is sometimes clinically obvious but some authors have proposed that a certain degree of inflammation in melanocytic nevi is independent of any mechanical or external factor [2].

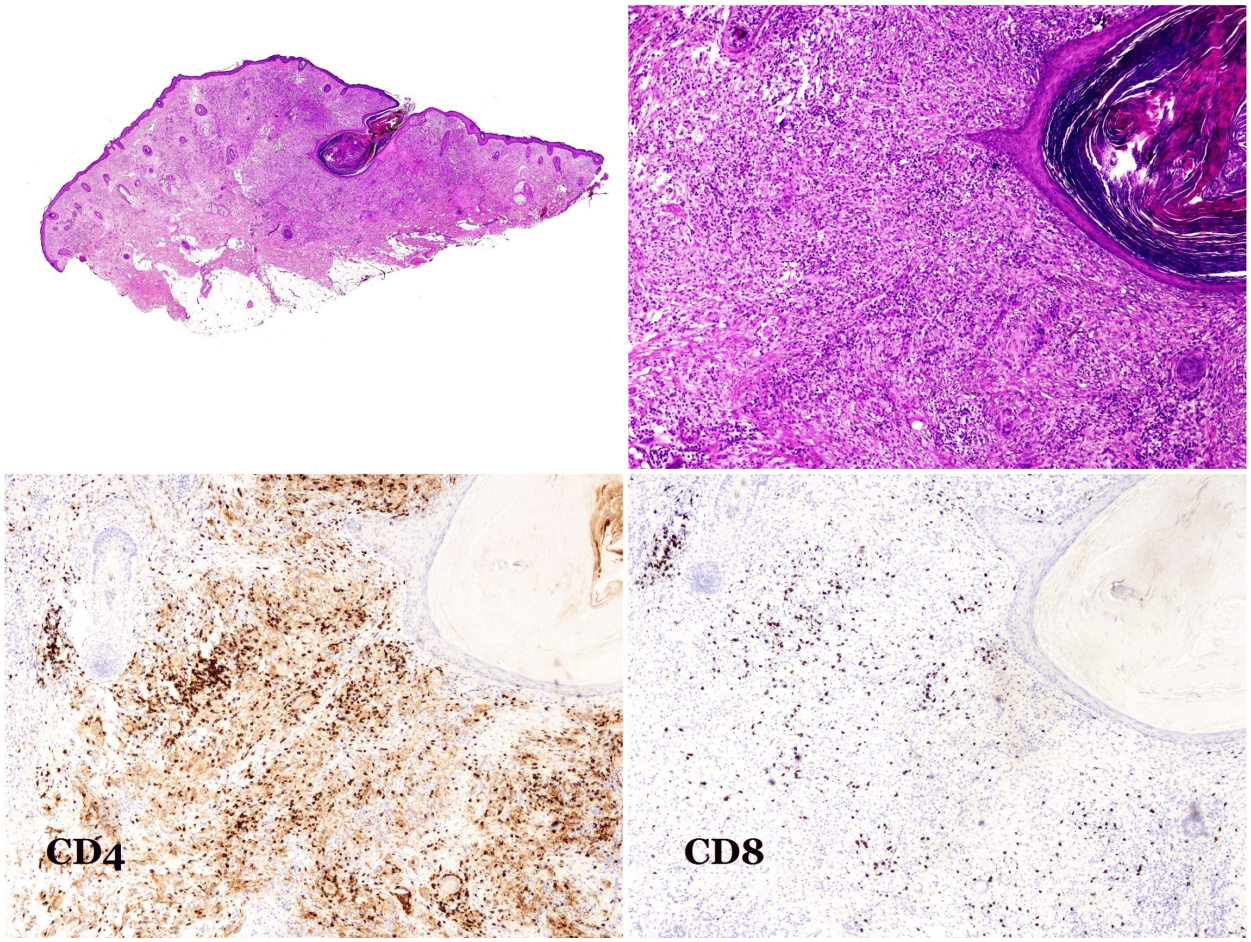

Figure 1 – ***Duperrat nevus showing an infundibular cyst adjacent to the melanocytic nevus. The inflammatory infiltrate is rich in CD4+ T-cells. Hematoxylin–Eosin (HE) staining: ×25, ×40; CD4 immunostaining, ×40; CD8 immunostaining, ×100.***

Usually, the inflammatory infiltrate in nevi is spare [3]. Benz *et al.* studied the presence of mononuclear inflammatory cells in 1054 melanocytic nevi [2] and concluded that "a weak to moderate lymphohistiocytic infiltrate is a common finding in early stages of evolving melanocytic nevus." They also found a "pronounced" infiltrate in 16% of cases and a "very strong" infiltrate in 1% of cases. "Pronounced" was defined as "abundant mononuclear cells within the upper dermis", while "very strong" was defined as "a dense mononuclear infiltrate filling the upper dermis." The authors concluded that such a large series excluded the possibility of trauma, irritation or perifolliculitis as a source of the infiltrate in most cases. However, cases with either pronounced or very strong inflammatory infiltrate were not numerous and therefore, in our opinion, trauma or external irritant was not excluded in those instances. The nature of the lymphocytic infiltrate mainly consisted of T-cells (CD20+ B-cells were virtually absent) [3] with a striking predominance of CD4+ T-cells over CD8+ T-cells [3, 4] (Figure 2).

Plasma cells in the inflammatory infiltrate of melanocytic nevi: not always an ominous sign

Evidence of plasma cells in the inflammatory infiltrate of a melanocytic lesion was traditionally considered a worrying feature in certain diagnostic contexts. The differential diagnosis between halo nevus and melanoma is an example: plasma cells are very few in halo nevus, but are easy to find in many melanomas [5, 6]. Plasma cells are also useful in the diagnosis of desmoplastic melanoma (with plasma cells) *versus* desmoplastic Spitz nevus (without plasma cells) [7]. However, a few plasma cells commonly accompany banal common melanocytic nevi. In one study, they were found in up to 41% of melanocytic nevi and were "easy to find" in around 10% of the cases [8] (Figure 3). The current study also adds new data on the abundance of plasma cells in Duperrat nevus as a common finding.

Meyerson nevus and Meyerson phenomenon: the "eczematous" type of inflammatory component

Meyerson nevus shows eczematous erythematous papulosquamous clinical changes superimposed on a melanocytic nevus [1, 9]. The term "Meyerson phenomenon" refers to a similar inflammatory reaction of lesions different from melanocytic nevi, such as keloids, seborrheic keratoses, carcinomas or dermatofibromas [10].

Many of the histopathological changes seen in Meyerson nevus involve the epidermis, such as spongiosis, vesiculation or parakeratosis. They are accompanied by an interstitial inflammatory infiltrate in the superficial dermis as well as by some exocytosis of lymphocytes [11–13].

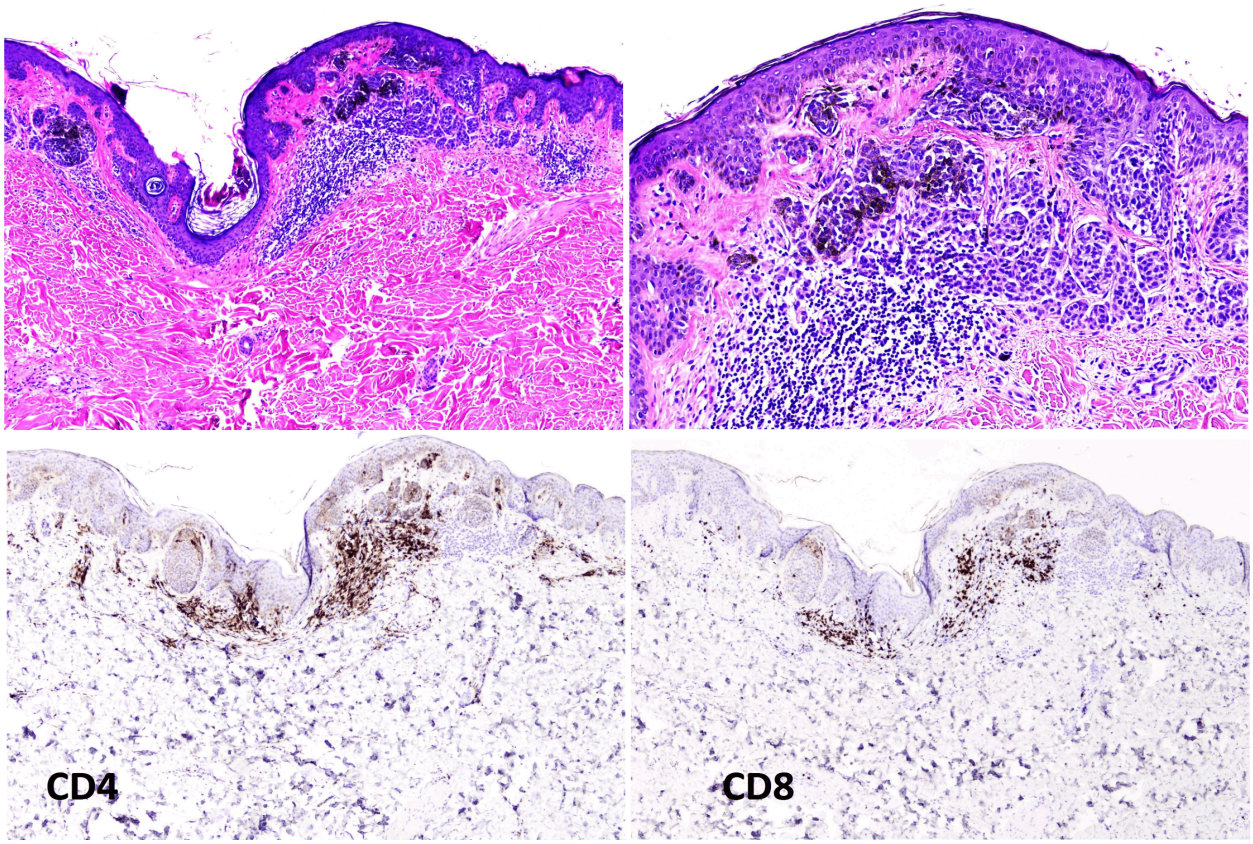

Figure 2 – ***Melanocytic nevus with mild nonspecific inflammatory response made of T-cells with a predominance of CD4+ cells. HE staining: ×40, ×200; CD4 immunostaining, ×40; CD8 immunostaining, ×40.***

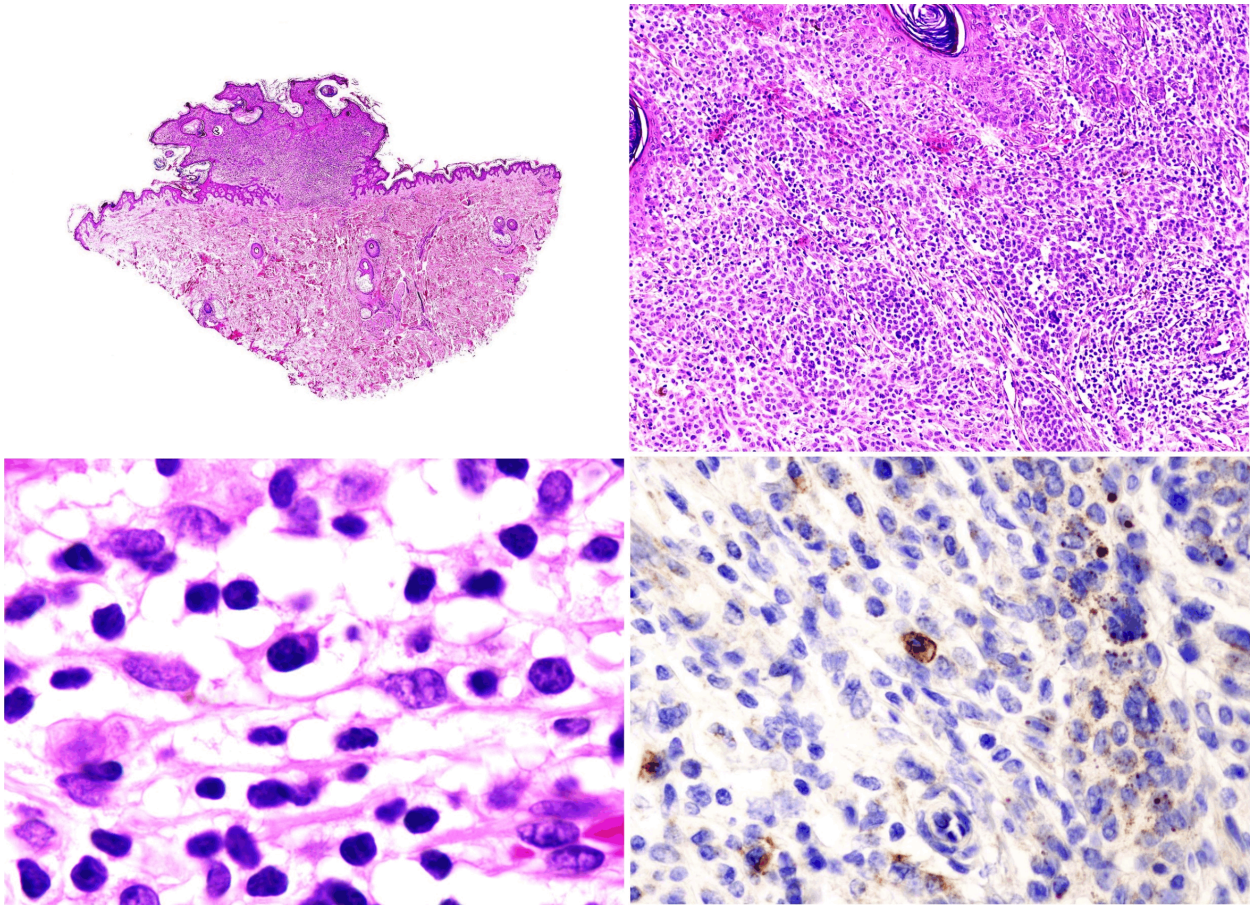

Figure 3 – ***Immunohistochemical study with CD138 in a heavily-inflamed intradermal nevus without atypia. Some occasional plasma cells are positive in the infiltrate. Plasma cells are easily found also in the routine HE staining: ×25, ×100, ×400; CD138 immunostaining, ×200.***

The etiology of the superimposed inflammatory changes of Meyerson nevus is not clear. It has been suggested that it could be the result of allergic contact dermatitis [11], a hypersensitivity reaction [14], or a response to solar exposure [11, 12, 15].

The inflammatory infiltrate is perivascular and mainly made up of CD4+ T-cells with a minority of CD8+ cells, but without signs of melanocytic regression [10, 16] (Figure 4). We have also had the opportunity to investigate the PD-1, BCL-6 and CD10 expression by the T-cells in two Meyerson nevi that we have recently examined. These three markers are considered indicative of follicular T-helper origin. About a third of the T-cells expressed PD-1 in both cases; however, they lack expression of BCL-6 and CD10.

Melanocytic nevus with regression: CD8+ T-cells rule

Regression is a complex phenomenon of active destruction of the melanocytic tumor, which has prognostic meaning in malignant melanoma. However, regression also happens in benign melanocytic nevi, so much so that it has been claimed that "we are born and we die without nevi" [17].

Several pathogenic mechanisms have been implicated in the regression of melanocytic nevi, but the most plausible is immunologic [18]. Some cases of regressing nevi have been induced by therapeutic antibodies [19].

Regression is histologically defined as: (*a*) a band-like accumulation of lymphocytes underlying the tumor, (*b*) lymphocytes breaking the tumor into nests that may contain apoptotic tumor cells and (*c*) a variable presence of melanophages [20].

Although it was traditionally claimed that regression in nevi is not accompanied by fibrosis (contrary to what occurs in melanoma), some studies have demonstrated that in the late stages of regressing nevi, there can be a peculiar type of fibrosis made of thin and delicate collagen bundles, randomly disorganized and accompanied by a low density of fibroblasts [21]. This contrasts with the thick collagen bundles of melanoma with regression. However, there is a type of regressing nevus in which the sclerosis can be prominent: the sclerosing nevus pseudomelanoma type [22–24]. Halo type is the best-known modality of regression, but there are several other patterns of regressing melanocytic nevi not related to the halo phenomenon [21].

The involved inflammatory cells in regressing melanocytic nevi are mainly CD8+ T-cells [20] and they are predominantly located in the periphery of the nevus [20] (Figure 5).

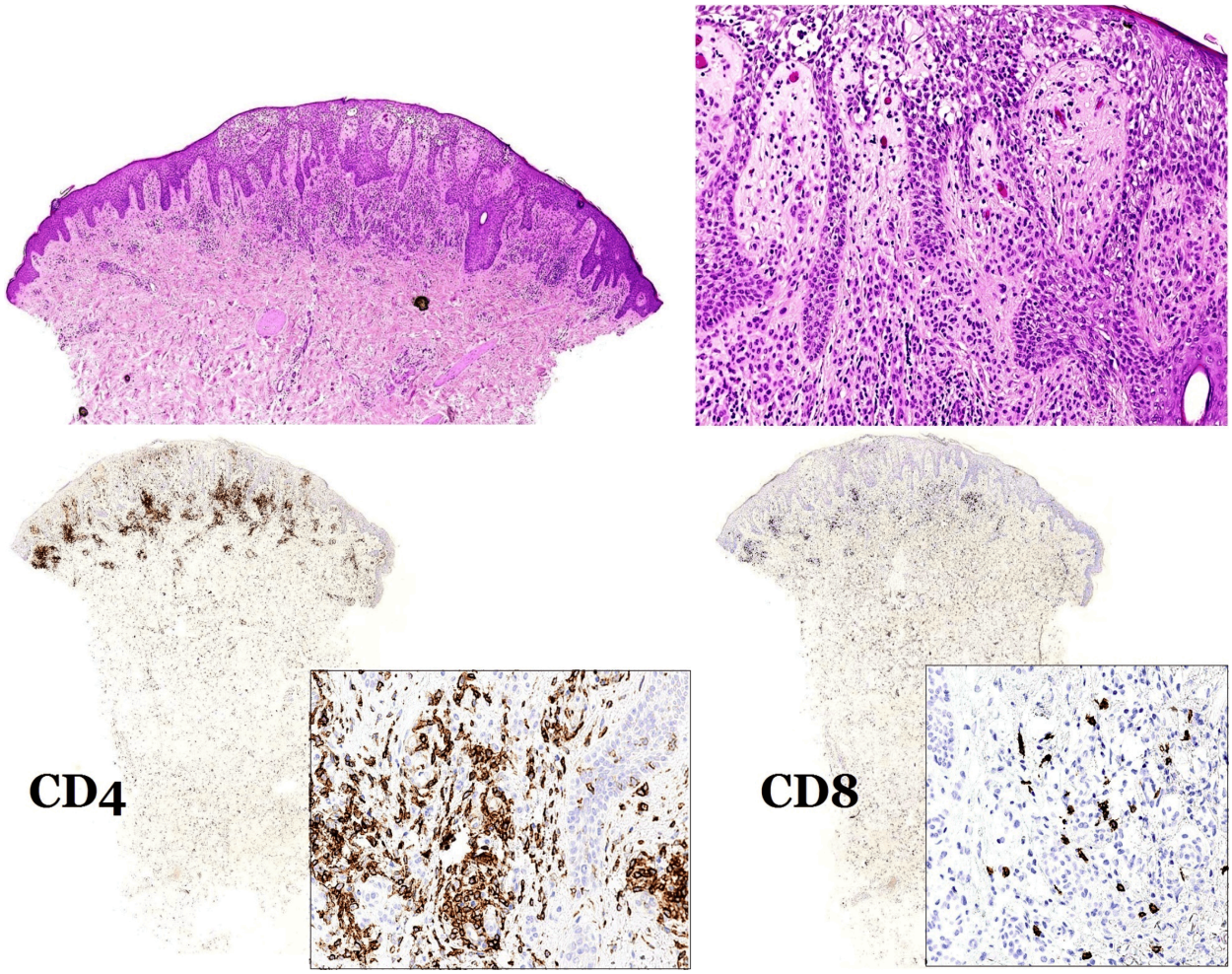

Figure 4 – ***Typical Meyerson nevus with prominent spongiotic changes in the epidermis and a prominent inflammatory infiltrate mainly made up of CD4+ T-cells. HE staining: ×25, ×100; CD4 immunostaining: ×25, ×100 (inset); CD8 immunostaining: ×25, ×100 (inset).***

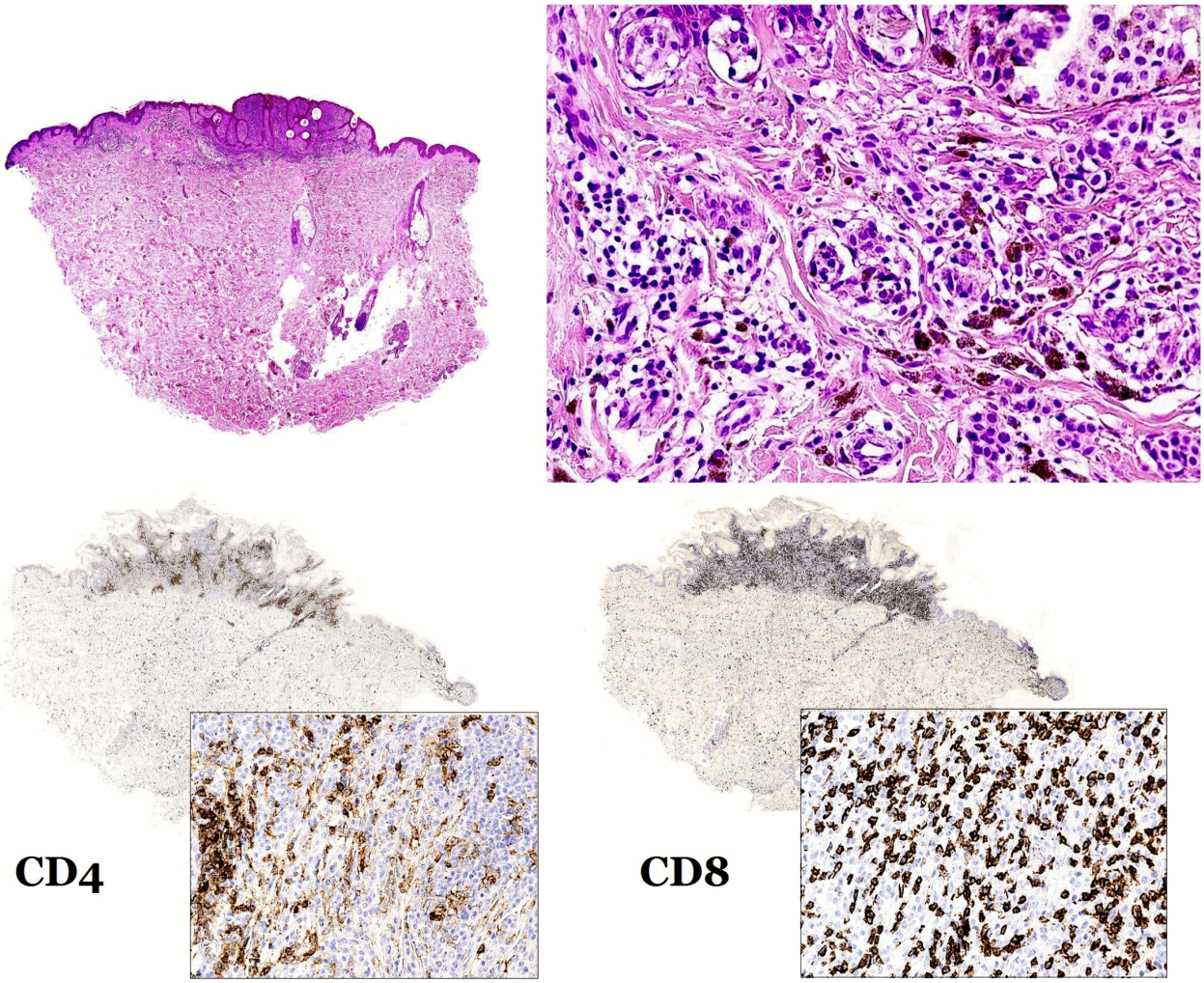

Figure 5 – ***A melanocytic nevus with many signs of regression, including lymphocytes disrupting groups of melanocytes, as well as many melanophages. The inflammatory infiltrate is prominent and mainly made up of CD8+ T cells. HE staining: ×25, ×200; CD4 immunostaining: ×25, ×100 (inset); CD8 immunostaining: ×25, ×100 (inset).***

Sutton (halo) nevus and halo reaction

Sutton nevus is a peculiar type of regressing melanocytic nevus, also known as halo nevus. Clinically, the nevus is surrounded by a peripheral hypopigmented halo. Cases in which the inflammatory reaction is histopathologically demonstrated, but there is no clinical evidence of a halo, are better referred as "halo reaction" cases.

The amount of the inflammatory infiltrate in halo nevus varies from moderate to dense, although some authors have defined halo nevus as "... a melanocytic lesion overwhelmed by a dense inflammatory infiltrate..." [25]. The amount of lymphocytes also varies with time and is only moderate in the final stages of regression [26, 27].

The inflammatory infiltrate is mainly made of T-cells (around 80% of cells) [28, 29]. Some authors claim that CD8+ T-cells are the majority in the infiltrate through all the stages of the lesion, varying from 75% in early lesions to more than 90% in advanced lesions. Other studies, however, have demonstrated equal proportions of CD4+ and CD8+ T-cells in some stages [27]. In general, it is accepted that the CD4:CD8 ratio can vary from 1:1 to 1:3 [27, 30, 31], but the infiltrate should never consist of a predominance of CD4+ lymphocytes. This contrasts with melanoma regression, in which the number of CD4+ cells overcomes the number of CD8+ T-cells [26, 27, 31–33].

The few studies available on the inflammatory infiltrate of Sutton nevi have focused on the CD4:CD8 ratio, without investigation of many of the cytotoxic markers. Bayer-Garner *et al.* included CD56 in their studies on halo nevus [27] and concluded that the number of CD56-positive cells in the early stages of halo nevus was increased over those seen in other regressing lesions such as benign lichenoid keratosis or keratoacanthoma [27].

Therefore, we decided to investigate several cytotoxic markers in the inflammatory infiltrate of nine cases of Sutton nevus, including CD8, Granzyme B, TIA-1, CD56 and CD57. Table 2 shows the clinical data of the cases included in the study (age and gender of the patients; location of the lesions) as well as the results of immunostaining for every marker.

Although CD8+ T-cells outnumbered the lymphocytic infiltrate (maximal CD4:CD8 40:60), most of the cells did not express cytotoxic markers. None of the markers was expressed by more than 10% of the lymphocytes and in many cases only scattered positive cells were evidenced (Figure 6). This was somewhat surprising because it has traditionally been claimed that the response evidenced in Sutton nevus is cytotoxic [27] based on the

predominance of CD8+ T-cells. However, it is currently known that there are several subsets of CD8+ T-cells and that the expression of cytolytic markers can vary according to their stage of differentiation [34]. Lack of expression of cytotoxic markers by a CD8+ T-cell population might be related to non-cytotoxic functional attributes such as activation, co-stimulation, regulation and homeostasis of T-cells, as well as to homing potential (chemotaxis and adhesion) [35]. We also know that tumoral regression is not exclusively cytotoxic and that there are several mechanisms through which a lymphocytic infiltrate can induce tumoral regression [36]. Our findings suggest that the regression of nevi might happen mainly through an alternative non-cytotoxic pathway.

Table 2 – ***Studied cases of Sutton***

Case No.	Age [years]	Gender	Location of the lesion	CD4/CD8 ratio [%]	Granzyme B	TIA-1	CD56	CD57
1.	33	M	Abdomen	40/60	Scattered cells	5%	Scattered cells	Scattered cells
2.	46	F	Chest	20/80	3%	5%	5%	3%
3.	11	F	Thigh	35/65	Scattered cells	10%	3%	1%
4.	22	F	Back	30/70	3%	10%	5%	3%
5.	21	M	Back	40/60	5%	5%	5%	3%
6.	15	F	Back	40/60	3%	3%	5%	5%
7.	25	M	Face	30/70	3%	5%	1%	7%
8.	40	M	Unknown	10/90	2%	5%	3%	3%
9.	10	F	Unknown	10/90	0%	0%	0%	Occasional (less than 1%)

M: Male; F: Female.

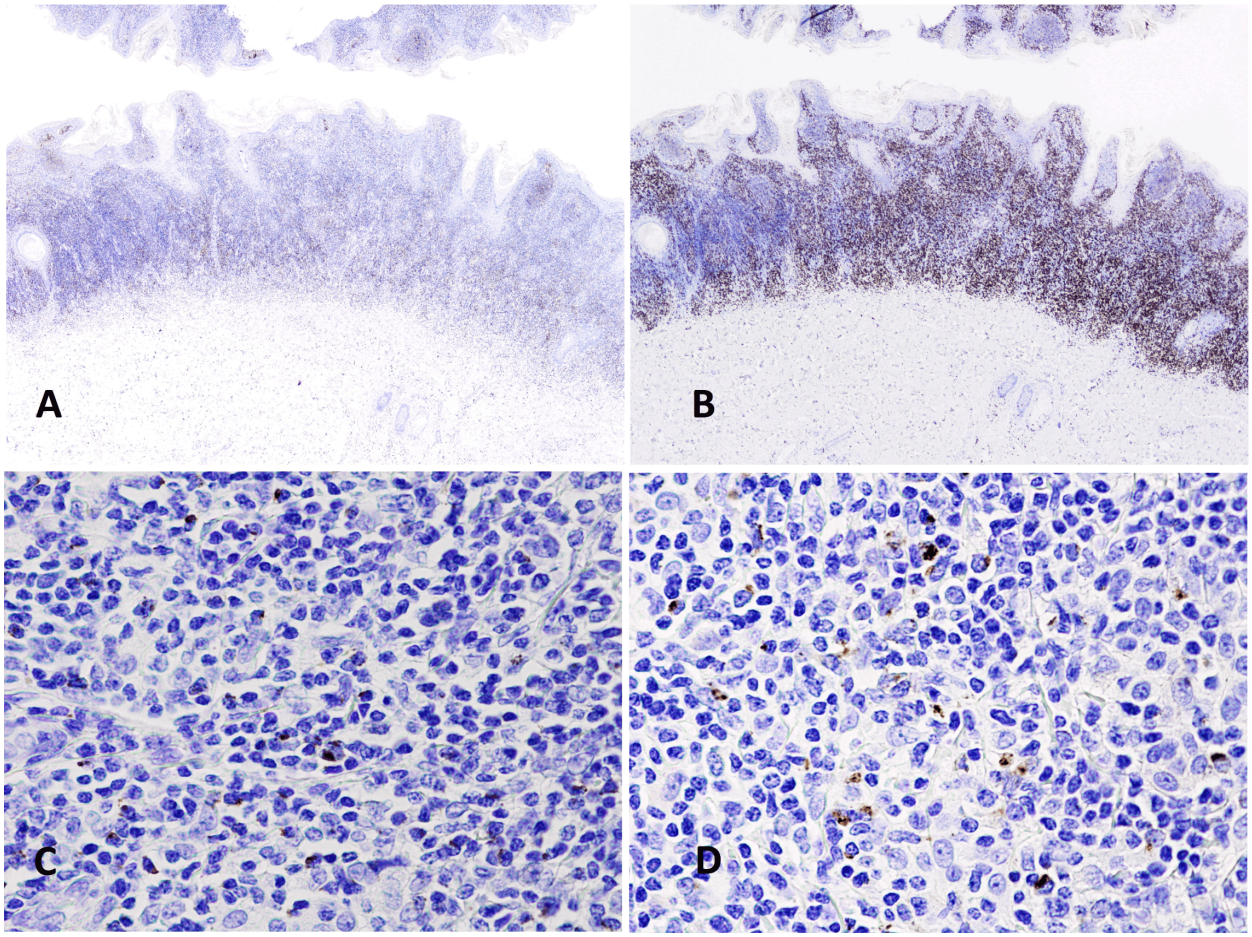

Figure 6 – ***Predominance of CD8+ (B) over CD4+ T-cells (A) in a Sutton nevus. TIA-1+ cells (C) as well as Granzyme B+ cells (D) are scattered. (A and B) ×25; (C and D) ×200.***

Wiesner nevus: not yet investigated

Wiesner nevus was recently identified as a melanocytic tumor with distinctive clinical, histopathological and molecular diagnostic criteria [37, 38]. This tumor is the cutaneous hallmark of a susceptibility syndrome associated with cutaneous or uveal melanoma, renal cell carcinoma, mesothelioma and other neoplasias [39–42]. The syndrome is associated with biallelic loss or inactivation of BAP1 in chromosome 3p21,38 which is a binding partner of BRCA1 and has been functionally implicated in DNA damage response [43, 44]. BAP-1 expression can be investigated by immunohistochemistry for the BAP-1 antibody; while most spitzoid nevi express this marker (Figure 7), Wiesner nevi do not. Moreover, up to 88% of Wiesner nevi carry BRAF mutations, which is unusual in Spitz nevi [37].

Wiesner nevi are made up of various atypical melanocytic populations in an irregular nested or sheet-like array, with the large epithelioid melanocyte being the leading cell type. There is often an accompanying inflammatory infiltrate, which is usually spare. However, the CD4:CD8 ratio of this infiltrate has not yet been investigated (verbal confirmation by Dr. Kutzner).

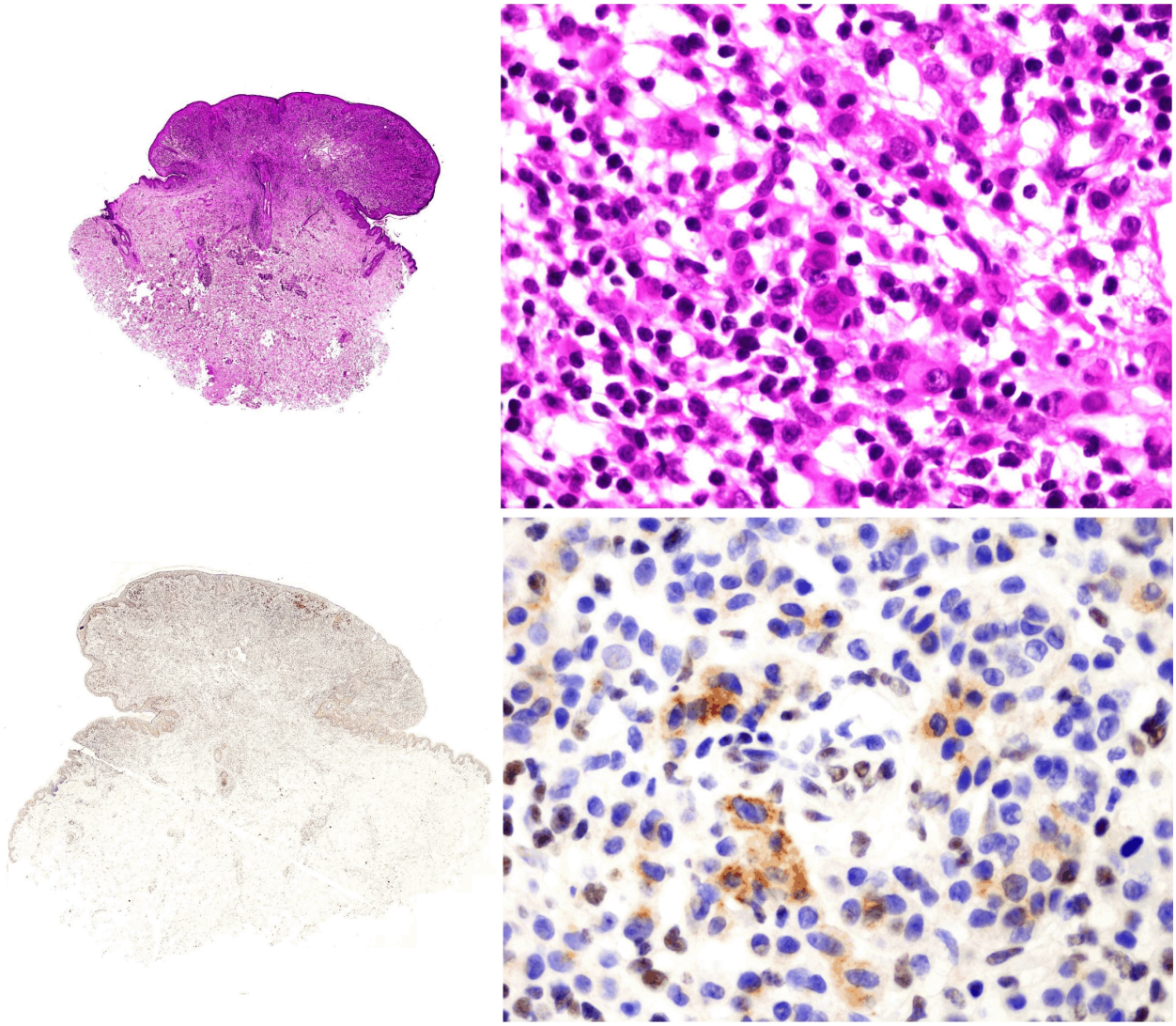

Figure 7 – ***Prominent inflammatory infiltrate in a melanocytic nevus in which many of the melanocytic cells showed epithelioid features. Immunostaining for BAP1 showed expression of the marker by many of the melanocytic cells. HE staining: ×25, ×400; BAP1 immunostaining: ×25, ×400.***

BAP1-negative atypical Spitz nevus

Apart from the nevi seen in the BAP1-related familial tumor syndrome, loss of BAP1 expression has been shown in sporadic cases of nevi that show histopathological features resembling the so-called atypical Spitz tumors [45]. About a third of these cases present with significant numbers of tumor-infiltrating lymphocytes ("halo-Spitz nevus"). However, CD4 and CD8 subpopulations have not been categorized in this type of tumor.

Conclusions

In summary, the inflammatory infiltrate accompanying the best-known types of nevi is as follows: Duperrat nevus: a mixed inflammatory reaction that includes histiocytes, foreign-body multinucleated giant cells, polymorphonuclears, lymphocytes (predominantly CD4+) and plasma cells (commonly abundant); common melanocytic nevus with reactive inflammatory infiltrate: an inflammatory infiltrate mainly made up of CD4+ T-cells; Meyerson nevus: an inflammatory infiltrate mainly made up of CD4+ T-cells. Some of these T-cells express PD-1 but other follicular T-helper markers, such as BCL-6 or CD10, are absent; melanocytic nevus with halo phenomenon: a dense inflammatory infiltrate with lymphocytes in a CD4:CD8 ratio varying from 1:1 to 1:3; Sutton nevus: a dense inflammatory infiltrate with lymphocytes in a CD4:CD8 ratio varying from 1:1 to 1:3. Most of these CD8+ T-cells do not express cytotoxic markers; Wiesner nevus: a spare lymphocytic infiltrate in most cases (nature of the infiltrate not yet investigated); BAP1-negative atypical Spitz nevus: a significant number of tumor-infiltrating lymphocytes (nature of the infiltrate not yet investigated).

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We also want to thank Dr. Kutzner for having shared with us the information that the nature of the inflammatory infiltrate of Wiesner nevi has not yet been investigated (when this report was written, at least).

References

[1] Fernandez-Flores A, *Eponyms, morphology, and pathogenesis of some less mentioned types of melanocytic nevi*, Am J Dermatopathol, 2012, 34(6):607–618.

[2] Benz G, Hölzel D, Schmoeckel C, *Inflammatory cellular infiltrates in melanocytic nevi*, Am J Dermatopathol, 1991, 13(6):538–542.

[3] Mourmouras V, Fimiani M, Rubegni P, Epistolato MC, Malagnino V, Cardone C, Cosci E, Nisi MC, Miracco C, *Evaluation of tumour-infiltrating CD4+CD25+FOXP3+ regulatory T cells in human cutaneous benign and atypical naevi, melanomas and melanoma metastases*, Br J Dermatol, 2007, 157(3):531–539.

[4] Nestor MS, Cochran AJ, *Identification and quantification of subsets of mononuclear inflammatory cells in melanocytic and other human tumors*, Pigment Cell Res, 1987, 1(1):22–27.

[5] Wayte DM, Helwig EB, *Halo nevi*, Cancer, 1968, 22(1):69–90.

[6] Jacobs JB, Edelstein LM, Snyder LM, Fortier N, *Ultrastructural evidence for destruction in the halo nevus*, Cancer Res, 1975, 35(2):352–357.

[7] Mooi WJ, Krausz T, *Spitz nevus versus spitzoid melanoma: diagnostic difficulties, conceptual controversies*, Adv Anat Pathol, 2006, 13(4):147–156.

[8] Fernandez-Flores A, *Plasma cell infiltrate in common acquired melanocytic nevus*, Acta Dermatovenerol Croat, 2008, 16(3): 158–163.

[9] Meyerson LB, *A peculiar papulosquamous eruption involving pigmented nevi*, Arch Dermatol, 1971, 103(5):510–512.

[10] Cook-Norris RH, Zic JA, Boyd AS, *Meyerson's naevus: a clinical and histopathological study of 11 cases*, Australas J Dermatol, 2008, 49(4):191–195.

[11] Weedon D, Farnsworth J, *Spongiotic changes in melanocytic nevi*, Am J Dermatopathol, 1984, 6(Suppl):257–259.

[12] Petit A, Viney C, Gaulier A, Sigal M, *Coexistence of Meyerson's with Sutton's naevus after sunburn*, Dermatology, 1994, 189(3): 269–270.

[13] Tauscher A, Burch JM, *Picture of the month – quiz case. Diagnosis: Meyerson phenomenon within a congenital melanocytic nevus*, Arch Pediatr Adolesc Med, 2007, 161(5):471–472.

[14] Brenan J, Kossard S, Krivanek J, *Halo eczema around melanocytic nevi*, Int J Dermatol, 1985, 24(4):226–229.

[15] Worret WI, *Halo eczema and nevus cell nevi (Meyerson nevi)*, Hautarzt, 1990, 41(5):262–264.

[16] Fernández Herrera JM, Aragües Montañés M, Fraga Fernández J, Diez G, *Halo eczema in melanocytic nevi*, Acta Derm Venereol, 1988, 68(2):161–163.

[17] Zalaudek I, Donati P, Catricalà C, Argenziano G, *"Sterbender Nävus" oder regressives Melanom?* Hautarzt, 2011, 62(4): 293–296.

[18] Ceballos PI, Barnhill RL, *Spontaneous regression of cutaneous tumors*, Adv Dermatol, 1993, 8:229–261; discussion 262.

[19] Libon F, Arrese JE, Rorive A, Nikkels AF, *Ipilimumab induces simultaneous regression of melanocytic naevi and melanoma metastases*, Clin Exp Dermatol, 2013, 38(3):276–279.

[20] McKay K, Moore PC, Smoller BR, Hiatt KM, *Association between natural killer cells and regression in melanocytic lesions*, Hum Pathol, 2011, 42(12):1960–1964.

[21] Martín JM, Rubio M, Bella R, Jordá E, Monteagudo C, *Regresión completa de nevos melanocíticos: correlación clínica, dermatoscópica e histológica de una serie de 13 casos*, Actas Dermosifiliogr, 2012, 103(5):401–410.

[22] Fabrizi G, Pennacchia I, Pagliarello C, Massi G, *Sclerosing nevus with pseudomelanomatous features*, J Cutan Pathol, 2008, 35(11):995–1002.

[23] Ferrara G, Amantea A, Argenziano G, Broganelli P, Cesinaro AM, Donati P, Pellacani G, Zalaudek I, Tomasini C, *Sclerosing nevus with pseudomelanomatous features and regressing melanoma with nevoid features*, J Cutan Pathol, 2009, 36(8):913–915; author reply 916.

[24] Massi G, *Sclerosing nevus vs regressing melanoma*, J Cutan Pathol, 2009, 36(8):916.

[25] Massi G, LeBoit P, Halo nevus. In: Massi G, LeBoit P (eds), *Histological diagnosis of nevi and melanoma*, Springer, Würzburg, Germany, 2004, 363–378.

[26] Zalaudek I, Argenziano G, Ferrara G, Soyer HP, Corona R, Sera F, Cerroni L, Carbone A, Chiominto A, Cicale L, De Rosa G, Ferrari A, Hofmann-Wellenhof R, Malvehy J, Peris K, Pizzichetta MA, Puig S, Scalvenzi M, Staibano S, Ruocco V, *Clinically equivocal melanocytic skin lesions with features of regression: a dermoscopic-pathological study*, Br J Dermatol, 2004, 150(1):64–71.

[27] Bayer-Garner IB, Ivan D, Schwartz MR, Tschen JA, *The immunopathology of regression in benign lichenoid keratosis, keratoacanthoma and halo nevus*, Clin Med Res, 2004, 2(2): 89–97.

[28] Bergman W, Willemze R, de Graaff-Reitsma C, Ruiter DJ, *Analysis of major histocompatibility antigens and the mononuclear cell infiltrate in halo nevi*, J Invest Dermatol, 1985, 85(1):25–29.

[29] Langer K, Konrad K, *Congenital melanocytic nevi with halo phenomenon: report of two cases and a review of the literature*, J Dermatol Surg Oncol, 1990, 16(4):377–380.

[30] Tokura Y, Yamanaka K, Wakita H, Kurokawa S, Horiguchi D, Usui A, Sayama S, Takigawa M, *Halo congenital nevus undergoing spontaneous regression. Involvement of T-cell immunity in involution and presence of circulating anti-nevus cell IgM antibodies*, Arch Dermatol, 1994, 130(8):1036–1041.

[31] Moretti S, Spallanzani A, Pinzi C, Prignano F, Fabbri P, *Fibrosis in regressing melanoma versus nonfibrosis in halo nevus upon melanocyte disappearance: could it be related to a different cytokine microenvironment?* J Cutan Pathol, 2007, 34(4):301–308.

[32] Patel A, Halliday GM, Cooke BE, Barnetson RS, *Evidence that regression in keratoacanthoma is immunologically mediated: a comparison with squamous cell carcinoma*, Br J Dermatol, 1994, 131(6):789–798.

[33] Tefany FJ, Barnetson RS, Halliday GM, McCarthy SW, McCarthy WH, *Immunocytochemical analysis of the cellular infiltrate in primary regressing and non-regressing malignant melanoma*, J Invest Dermatol, 1991, 97(2):197–202.

[34] Takata H, Takiguchi M, *Three memory subsets of human CD8+ T cells differently expressing three cytolytic effector molecules*, J Immunol, 2006, 177(7):4330–4340.

[35] Appay V, van Lier RA, Sallusto F, Roederer M, *Phenotype and function of human T lymphocyte subsets: consensus and issues*, Cytometry A, 2008, 73(11):975–983.

[36] Elston DM, *Mechanisms of regression*, Clin Med Res, 2004, 2(2):85–88.

[37] Wiesner T, Obenauf AC, Murali R, Fried I, Griewank KG, Ulz P, Windpassinger C, Wackernagel W, Loy S, Wolf I, Viale A, Lash AE, Pirun M, Socci ND, Rütten A, Palmedo G, Abramson D, Offit K, Ott A, Becker JC, Cerroni L, Kutzner H, Bastian BC, Speicher MR, *Germline mutations in BAP1 predispose to melanocytic tumors*, Nat Genet, 2011, 43(10): 1018–1021.

[38] Llamas-Velasco M, Pérez-Gónzalez YC, Requena L, Kutzner H, *Histopathologic clues for the diagnosis of Wiesner nevus*, J Am Acad Dermatol, 2014, 70(3):549–554.

[39] Dey A, Seshasayee D, Noubade R, French DM, Liu J, Chaurushiya MS, Kirkpatrick DS, Pham VC, Lill JR, Bakalarski CE, Wu J, Phu L, Katavolos P, LaFave LM, Abdel-Wahab O, Modrusan Z, Seshagiri S, Dong K, Lin Z, Balazs M, Suriben R, Newton K, Hymowitz S, Garcia-Manero G, Martin F, Levine RL, Dixit VM, *Loss of the tumor suppressor BAP1 causes myeloid transformation*, Science, 2012, 337(6101):1541–1546.

[40] Murali R, Wiesner T, Scolyer RA, *Tumours associated with BAP1 mutations*, Pathology, 2013, 45(2):116–126.

[41] Henderson DW, Reid G, Kao SC, van Zandwijk N, Klebe S, *Challenges and controversies in the diagnosis of mesothelioma: Part 1. Cytology-only diagnosis, biopsies, immunohistochemistry, discrimination between mesothelioma and reactive mesothelial hyperplasia, and biomarkers*, J Clin Pathol, 2013, 66(10):847–853.

[42] Popova T, Hebert L, Jacquemin V, Gad S, Caux-Moncoutier V, Dubois-d'Enghien C, Richaudeau B, Renaudin X, Sellers J,

Nicolas A, Sastre-Garau X, Desjardins L, Gyapay G, Raynal V, Sinilnikova OM, Andrieu N, Manié E, de Pauw A, Gesta P, Bonadona V, Maugard CM, Penet C, Avril MF, Barillot E, Cabaret O, Delattre O, Richard S, Caron O, Benfodda M, Hu HH, Soufir N, Bressac-de Paillerets B, Stoppa-Lyonnet D, Stern MH, *Germline BAP1 mutations predispose to renal cell carcinomas*, Am J Hum Genet, 2013, 92(6):974–980.

[43] Matsuoka S, Ballif BA, Smogorzewska A, McDonald ER 3rd, Hurov KE, Luo J, Bakalarski CE, Zhao Z, Solimini N, Lerenthal Y, Shiloh Y, Gygi SP, Elledge SJ, *ATM and ATR substrate analysis reveals extensive protein networks responsive to DNA damage*, Science, 2007, 316(5828):1160–1166.

[44] Stokes MP, Rush J, Macneill J, Ren JM, Sprott K, Nardone J, Yang V, Beausoleil SA, Gygi SP, Livingstone M, Zhang H, Polakiewicz RD, Comb MJ, *Profiling of UV-induced ATM/ATR signaling pathways*, Proc Natl Acad Sci U S A, 2007, 104(50): 19855–19860.

[45] Wiesner T, Murali R, Fried I, Cerroni L, Busam K, Kutzner H, Bastian BC, *A distinct subset of atypical Spitz tumors is characterized by BRAF mutation and loss of BAP1 expression*, Am J Surg Pathol, 2012, 36(6):818–830.

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