Original article

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Atypical Spitz tumours: an epidemiological, clinical and dermoscopic multicentre study with 16 years of follow-up

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Summary

Background. Atypical Spitz tumours (ASTs) are regarded as an intermediate category distinguished from prototypical Spitz naevus by presenting one or more atypical features and often by an uncertain malignant potential. Clinical and dermoscopic features may play a relevant role in the diagnostic approach.

Aim. To evaluate the clinical and dermoscopic features of ASTs, and their evolution over time.

Methods. This was a descriptive, multicentre study of the clinical and dermoscopic characteristics of ASTs. Data on clinical and dermoscopic characteristics, histopathology, local extension, therapy and follow-up, lymph node staging, complete lymph node dissection, and outcome were collected from the databases of four Italian Dermatology Units for the period 2004–2021.

Results. The study population consisted of 99 patients (62 female, 37 male) with a histologically confirmed diagnosis of AST, including age at presentation ranged from 2 to 70 years (mean 28.1 years, median 24 years). Of the 99 patients, 29 (29.3%) underwent sentinel lymph node biopsy, which showed evidence of micrometastases in three cases (10.3%); all three patients underwent complete lymph node dissection with no evidence of further metastasis. Considering the whole study population, the clinical outcome was excellent, as all of the patients have no evidence of recurrence or distant metastasis. The follow-up period ranged from 6 to 216 months (mean 81.6 months, median 78 months). In addition, we collected data on the clinical and dermoscopic features of 26 lesions. The most frequent dermoscopic pattern observed was the multicomponent pattern (34.6%), followed by homogeneous (26.9%) and nonspecific (23.2%). In 66.7% of amelanotic ASTs, we observed glomerular (coiled) vessels uniformly distributed within the entire lesion, without asymmetry.

Conclusion. The results of our study with a long follow-up show no recurrence or distant metastases, confirming the good clinical outcome, even in the case of sentinel lymph node positivity. From a diagnostic point of view, our series identified a typical dermoscopic picture for amelanotic ASTs, with a glomerular vascular pattern

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throughout the lesion in the absence of other dermoscopic parameters, making the correct diagnosis possible.

Introduction

Spitz naevi are uncommon acquired naevi composed of epithelioid and/or spindle melanocytes.[1] The term 'Spitz naevus' is reserved for lesions lacking atypical features and a very low risk of neoplastic progression. Atypical Spitz tumours (ASTs) are now regarded as an intermediate category distinguished from prototypical Spitz naevus by presenting one or more atypical features and often by an uncertain malignant potential.[2] They usually present as dome-shaped, pink to reddish-brown papules or nodules, which are > 5–10 mm in diameter and mostly located on the legs.[2,3]

Histopathology, in conjunction with distinctive genetic alterations, including kinase fusions, is the gold standard for the diagnosis of AST. However, in challenging cases, a diagnostic pathological consensus is difficult to achieve. Thus, clinical and dermoscopic features may play a relevant role in the diagnostic approach. To date, only a few studies have fully addressed these findings. Ludgate *et al.*[4] reported the clinical presentation of 67 ASTs, identifying a slight female predominance and a tendency to occur at a young age. Most of the lesions were described as amelanotic, and the most common location was the leg followed by the head and neck.[3] A few years later, Moscarella *et al.*[5] described the clinical and dermoscopic characteristics of 55 ASTs: the mean age at diagnosis was 20.8 years, the majority of ASTs presented as a pigmented nodular lesion, and most cases were dermoscopically characterized by a multicomponent pattern, followed by a no-specific pattern.

To improve the diagnostic accuracy and optimal management of AST, we performed a study of a large series of patients with AST retrieved from the database of four dermatology units in Italy (Florence, Livorno, Perugia and Pistoia) from October 2004 to January 2021. We assessed the clinical and dermoscopic features of the tumours, and the outcome of the patients.

Methods

This study was approved by the Institutional Review Board of University of Florence, Italy. Informed consent was obtained from all participants both for study participation and for publication of case details and images.

Study design

This descriptive, multicentre study of the clinical and dermoscopic characteristics of ASTs that were surgically excised and histopathologically confirmed. Data on the clinical and dermoscopic characteristics, histopathology, local extension, therapy and follow-up, lymph node staging [clinical involvement, sentinel lymph node (SLN) procedure, and complete lymph node dissection (CLND)], and outcome were collected from the databases of four Italian Dermatology Units (Firenze, Pistoia, Livorno and Perugia). The inclusion criterion was the availability of the data of a histopathologically diagnosed AST or atypical Spitz naevus between October 2004 and January 2021. Patients without relevant medical records were excluded.

Dermoscopy

All lesions were examined by dermatopathologists specialized in the diagnosis of melanocytic skin tumours. The equipment used for the dermoscopic examination consisted of a hand-held dermatoscope (Delta 20; Heine Optotechnick, Herrsching, Germany). Both clinical and dermoscopic images of all lesions were captured with a high-resolution compact digital photographic camera (E-520; Olympus, Tokyo, Japan; 7.1 MP, 3.8 optical zoom lens, focal length 28–105 mm in 35-mm format, and maximum lens aperture f/2.8–f/5.8). Dermoscopic images were captured using an instrument (Dermaphot; Heine Optotechnick) that connects the dermatoscope to the camera to generate reproducible, high-quality dermoscopic pictures at 10-fold magnification and exports them as JPG format files. These clinical and dermoscopic images and the data were stored on a common Windows-based (Microsoft Corp., Redmond, WA, USA) personal computer.

Assessment

Three investigators (FS, IS, VDG) with expertise in pigmented lesions and dermoscopy and no knowledge of the clinical history of the lesion independently analysed the archived digital dermoscopic images and completed a printed questionnaire (Supplementary Data S1) to categorize the lesions according to typical

dermoscopic pattern analysis. These dermatologists possessed identical levels of training and experience in dermatology, each with > 5 years of practice in dermoscopy. The dermoscopic pattern and the presence or the absence of dermoscopic features in a given lesion were defined by the agreement of at least two of the three dermoscopists. Following the report by Menzies *et al.*,[6] each lesion was defined as amelanotic (absence of pigmentation), hypomelanotic (pigmentation involving < 50% of the lesion) or pigmented (pigmentation involving > 50% of the lesion).

Statistical analyses

Descriptive analyses were performed to summarize the number and proportion of patients by demographics, tumour characteristics, clinical management and outcome.

Results

The data are available on request from the authors.

Demographics

The study population consisted of 99 patients [62 females (62.6%) and 37 males (37.4%)] with a histologically confirmed diagnosis of AST. Age at presentation ranged from 2 to 70 years (mean 28.1 years, median 24 years), with the majority (58.6%) of patients being in the age range 18–50 years and with the second peak seen in patients < 18 years (30.4%). The mean age was 29.7 years for females and 25.3 years for males, respectively. Anatomical site was as follows: legs (48.7%), trunk (25.2%), arms (14.1%), head and neck (8%), and acral area (4%) (Table 1).

Metastases

All patients were asymptomatic, and none showed signs of nodal metastases at the time of diagnosis. All patients underwent wide local excision with 10-mm margins, but despite this, 35 patients (35.7%) also needed peripheral resection with 5-mm margins, and of these, 29 underwent SLN biopsy (SLNB), which showed evidence of micrometastases in three cases (10.3%). These three patients received complete lymph node dissection, with no evidence of further metastasis. Until relatively recently, specific guidelines for the management of these lesions were not available, thus decisions concerning SLNB and management of regional lymph nodes were made by a multidisciplinary team and discussed with both patients and caregivers.

Table 1 Clinical features and outcome of the 99 patients assessed.

Parameter	*n*	%
Sex		
Male	37	67.4
Female	62	62.6
Age at presentation, years		
≤ 12	15	15.2
12–18	15	15.2
18–50	58	58.6
> 50	11	11
Tumour location		
Head and neck	8	8
Trunk	25	25.2
Arms	14	14.1
Legs	48	48.7
Acral	4	4
Radical excision		
Yes	35	35.7
No	63	64.3
SLNB		
Positive	3	10.3[a]
Negative	26	89.7[a]
CLND		
Positive	0	0[b]
Negative	3	100[b]

CLND, complete lymph node dissection; SLNB, sentinel lymph node biopsy. [a]Of the patients who underwent SLNB; [b]of the patients who underwent CLND.

Fluorescence-based investigations

Of the 99 patients, 19 (19.6%) were also assessed by fluorescence *in situ* hybridization (FISH) using a melanoma probe, and genetic alterations were found in three cases (15.8%) according to the previously described cutoff.[7] In these three cases, 9p21 homozygous deletion by FISH was not found. One of the three patients underwent SLNB, which showed no evidence of disease.

During follow-up of the 99 patients, 2 (2%) developed new primary cutaneous melanoma (CM) in other sites, and 2 other patients (2%) had nonmelanoma skin cancer excised; all 4 cases are free of disease.

Considering the whole study population, the clinical outcome was excellent, as all patients are alive at time of writing, with no evidence of recurrence or distant metastasis. The follow-up period ranged from 6 to 216 months (mean 81.6 months, median 78 months).

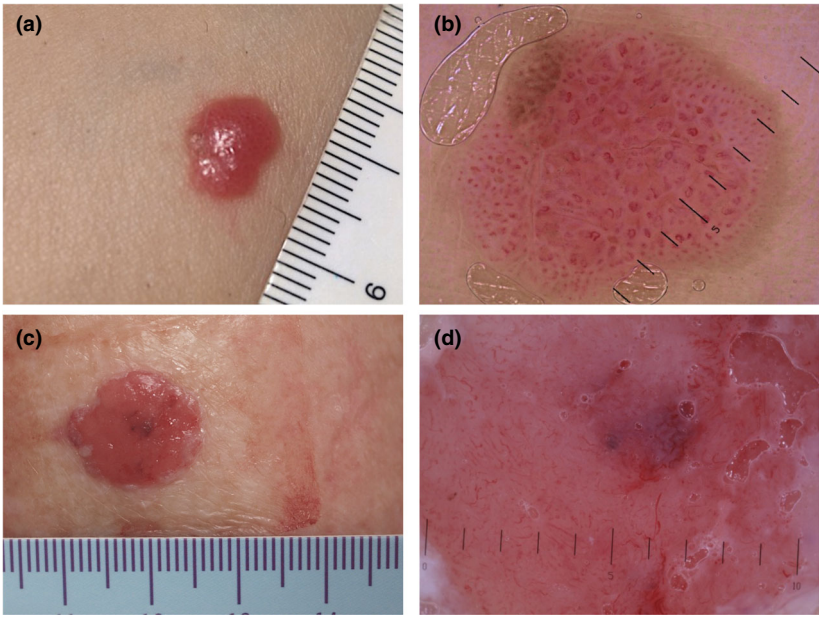

Figure 1 Clinical and dermoscopic images of amelanotic atypical Spitz tumour (AST) and malignant melanoma (MM) (scale bars are in mm). (a,b) Amelanotic AST on the leg of a 35-year-old woman: (a) clinical presentation; (b) dermoscopy showing glomerular (coiled) vessels uniformly distributed within the entire lesion, without asymmetry. (c,d) Amelanotic MM (Breslow thickness 2.6 mm, six mitoses) on the arm of a 72-year-old man: (c) clinical presentation; (d) dermoscopy showing pinkish background, milky-red areas and atypical vascular pattern with polymorphic vessels. Original magnification (a–d) × 10.

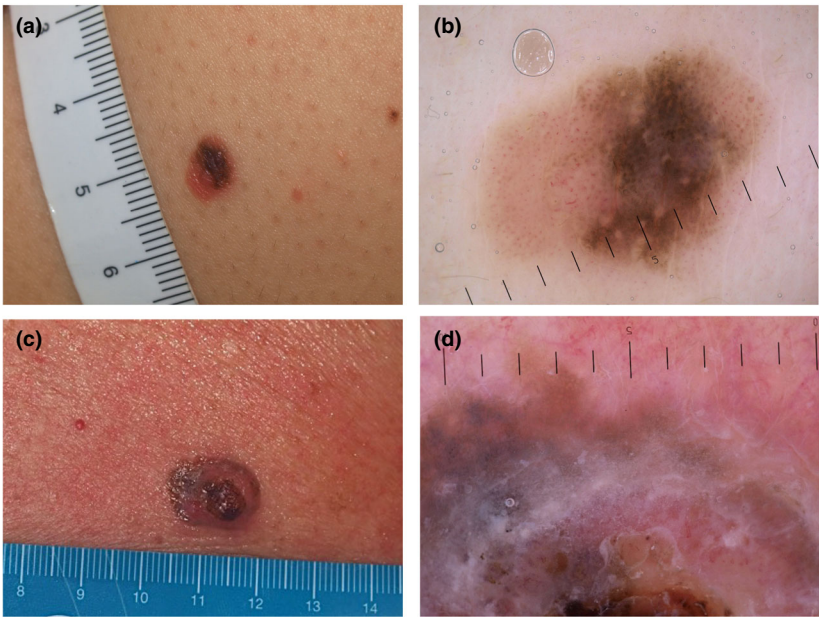

Figure 2 Clinical and dermoscopic images of amelanotic atypical Spitz tumour (AST) and malignant melanoma (MM) (scale bars are in mm). (a,b) Hypopigmented AST on the buttock of a 19-year-old woman: (a) clinical presentation; (b) dermoscopy shows a combination of glomerular vessels in amelanotic areas and cobblestone pattern in pigmented sections. (c,d) Hypopigmented MM (Breslow thickness 3.3 mm, 13 mitoses) on the scapular region of a 74-year-old man: (c) clinical presentation; (d) dermoscopy reveals a polymorphous vascular pattern, blue–whitish veil, shiny white structures, and atypical pigment network together with focal ulceration within the lesion. Original magnification (a–d) × 10.

Clinical and dermoscopic features

Data on the clinical and dermoscopic features were collected for 26 lesions. Clinically, the majority of AST presented as papular lesions (73.1%), followed by macules (19.2%) and nodules (7.7%). Nearly a third of ASTs 30.8% were amelanotic (Fig. 1a,b) and 15.4% hypopigmented (Fig. 2a,b), while half were pigmented (53.8%) (Figs 3a,b and 4a,b), whereas lesion size ranged from 4 to 148 mm (mean 8.58 mm; median 88 mm).

The most frequent dermoscopic pattern observed was the multicomponent pattern (34.6%), followed by homogeneous (26.9%) and nonspecific (23.2%). A globular pattern was described in three cases (11.5%) and a reticular pattern in one patient (3.8%). The vascular pattern, when evident, consisted of glomerular

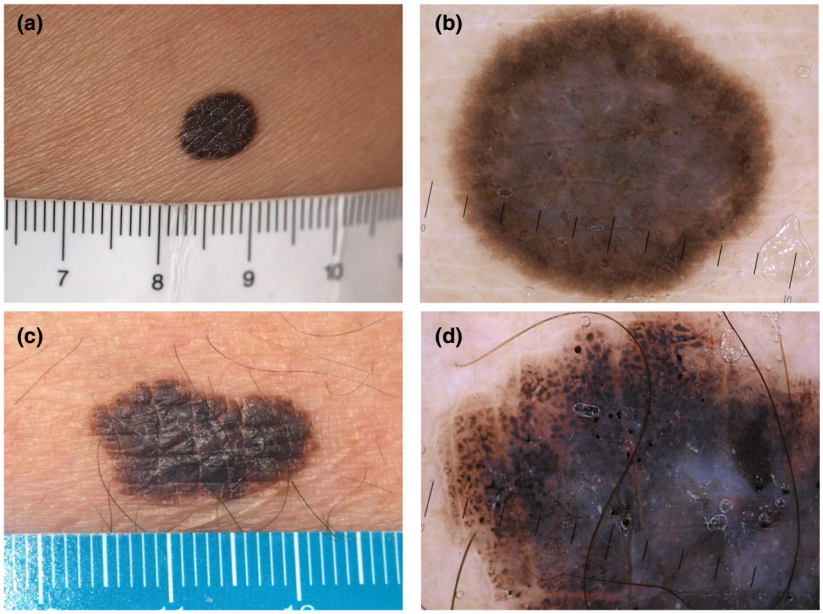

Figure 3 Clinical and dermoscopic images of amelanotic atypical Spitz tumour (AST) and malignant melanoma (MM) (scale bars are in mm). (a,b) Pigmented AST on the buttock of a 63-year-old woman: (a) clinical presentation; (b) dermoscopy showing a peripheral reticular pattern together with reticular depigmentation and a blue–white veil. (c,d) Pigmented MM (Breslow thickness 0.3 mm) on the thigh of an 81-year-old man: (c) clinical presentation; (d) Dermoscopy showing a multicomponent pattern with atypical network, globules that are irregular in both size and form, and a blue–whitish veil. Original magnification (a–d) × 10.

(34.6%), polymorphic (19.2%), linear (7.7%) or dotted (3.8%) vessels. In 66.7% of amelanotic ASTs, we observed glomerular (coiled) vessels uniformly distributed within the entire lesion, without asymmetry. Other dermoscopic features evaluated were vessel distribution, streaks, homogeneous pigmentation, superficial black network, brown globules, inverse network, crystalline structures, network, blue–white veil and regression.

Discussion

Owing to their rarity, little is known about the long-term clinical behaviour of AST, and only a few studies have investigated their specific clinical and dermatoscopic features.[5] Our prospective multicentre study provides relevant information concerning the epidemiology and the clinical and dermoscopic presentation of ASTs, focusing on patient outcome upon a 16-year follow-up period.

As the terminology and recommendations for managing these tumours have changed through the years,[8–10] our data reflect the different approaches proposed and strengthen the published literature. In particular, in the early 2000s, SLNB was strongly advised because several studies had demonstrated that 29–50% of patients with ASTs had sentinel node involvement.[11] In our cohort, SLNB was performed in 29.3% of patients, with a positive rate of 10.3%, who then underwent CLND, but none of these patients experienced metastases or disease recurrence.

Our data, which reflect 16 years of follow-up in a cohort of 99 patients, show a favourable prognosis with no event of widespread distant metastasis or recurrence, even in cases with positive SLNB findings. Our results support previous observations[12] showing that SLNB positivity does not affect long-term outcome. In our view, the correct management of ASTs consists of wide local excision with 5–10 mm clear margins, then follow-up with clinical evaluation of the body surface and locoregional lymph node sonography every 6 months for at least 5 years. SLNB is not currently recommended for these tumours; however, sentinel node staging may be considered in highly selected, diagnostically complex cases with lesions > 1 mm thick (e.g. when a malignant Spitz tumour or Spitz melanoma can not be excluded by histopathological examination even upon referral/expert consultation).[13]

In this study, we also aimed to investigate the clinical and dermoscopic presentation of such tumours, which might be helpful to guide the correct histopathological diagnosis in difficult cases. To our knowledge, ASTs are chameleonic lesions, making clinical and dermoscopic definition difficult.[5,14] However, although specific dermoscopic criteria are not yet available, certain features might be helpful to better define the clinical orientation. We found that clinically, ASTs usually present as papular lesions, either pigmented, hypopigmented or nonpigmented. In our series, the diagnosis was easier for truly amelanotic tumours, owing to their peculiar vessel distribution

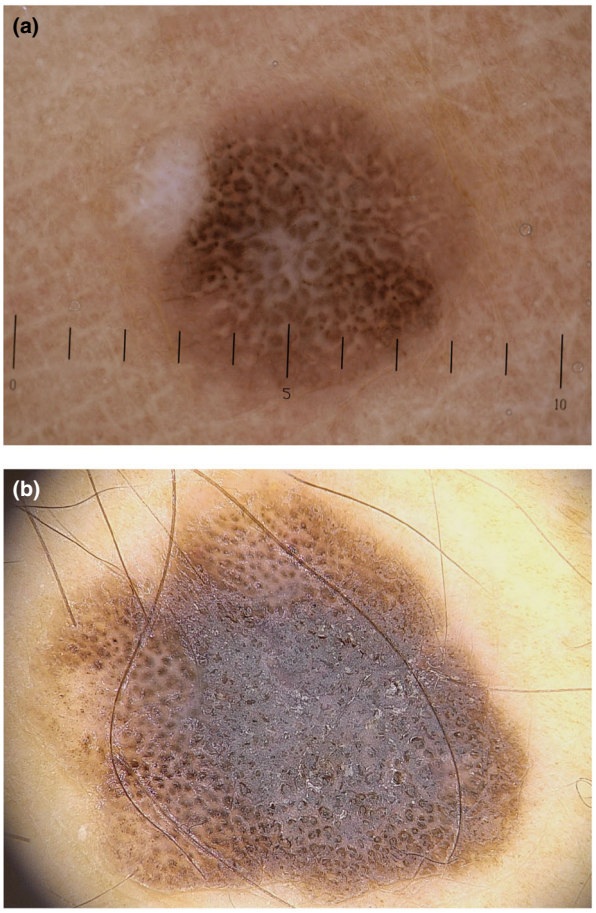

Figure 4 (a,b) Dermoscopic images of pigmented atypical Spitz tumour, showing brownish densely aggregated globules compressing each other, creating shapes (a) reminiscent of cobblestones homogeneously distributed throughout the lesion on the legs of a 9-year-old boy, and (b) simulating a sort of coarse pigment network on the foot of a 26-year-old woman. Original magnification (a,b) × 10.

and morphology that, upon histopathological examination, correlates with dilated vessels filled with erythrocytes in the superficial dermis (Fig. 5a). In fact, in 66.7% of amelanotic ASTs, we observed glomerular (coiled) vessels uniformly distributed within the entire lesion, without asymmetry (Fig.1b). This particular morphology and distribution of the vascular pattern allowed us to distinguish between these ASTs and achromic melanoma, which presents a different atypical and asymmetrical vascular pattern[15] (Fig. 1).

The differential diagnosis with nonmelanocytic lesions such as Bowen disease (BD) and Spitz naevus deserves closer inspection. In fact, while the presence of glomerular vessels is classically related to BD,[16] they usually appear clustered and slightly larger than in ASTs, and also show a scaly surface that is not evident in spitzoid lesions. Moreover, AST is typically greater in dimensions than Spitz naevus, and although the vessel morphology may be confused with that of dotted vessels when viewed with the naked eye, dermoscopy reveals a glomerular distribution in ASTs that has never been described in Spitz naevus.[17] Patient data must be taken into account in the differential diagnosis. For example, BD is seen in older patients and frequently on photodamaged skin, unlike AST, which can be seen in those < 18 years old (30% of cases) and in young adults (59% of cases). The remaining cases could not be clearly differentiated from amelanotic MM, as they presented with a nonspecific vascular pattern.

On the other hand, pigmented ASTs are more challenging[18] (Fig. 3). Although the distinction between pigmented ASTs and CM is difficult to achieve in most cases, we have highlighted some features that may be of interest. In particular, in 28.6% of pigmented ASTs, we found the presence of brownish densely aggregated

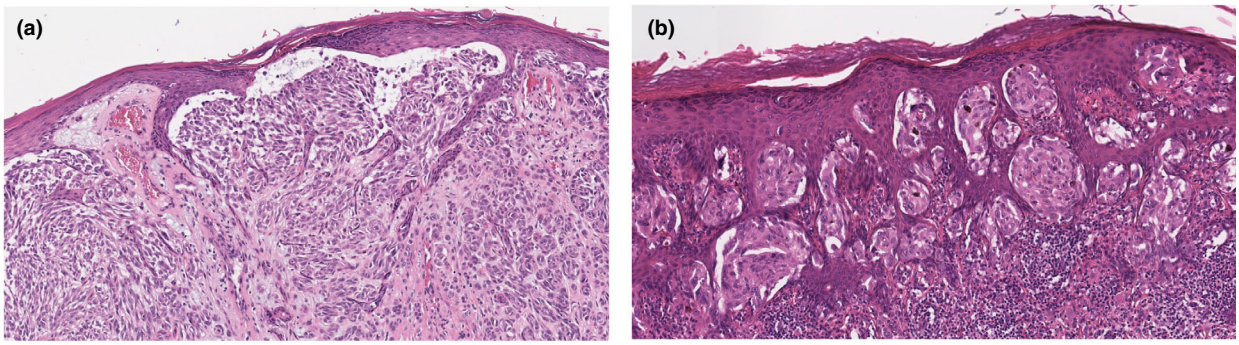

Figure 5 (a,b) Histological images of atypical Spitz tumours (ASTs). (a) Amelanotic AST, showing densely cellular aggregates of atypical spindle and epithelioid melanocytes devoid of pigment, with epidermal consumption and clefting. Numerous dilated vessels replete with erythrocytes were also present in the superficial dermis. (b) Pigmented AST, showing confluent nests of atypical epithelioid melanocytes with abundant eosinophilic cytoplasm and enlarged nuclei with prominent nucleoli. Foci of melanin pigment were present in scattered melanocytes and rare melanophages. The epidermis was hyperplastic and there was a prominent perilesional lymphocytic infiltrate. Original magnification (a,b) × 100.

globules compressing each other, creating shapes reminiscent of cobblestones homogeneously distributed throughout the lesion (Fig. 4). Upon histopathological examination, pigmented ASTs show epidermal hyperplasia and confluent nests of atypical epithelioid melanocytes with scattered melanin depositions (Fig. 5b). This feature, together with reticular depigmentation, seems typical for this subset of melanocytic tumours. Nonetheless, the presence of a cobblestone pattern is also one of the hallmarks of congenital melanocytic naevi (CMN).[19] However, this is typically associated with other specific CMN dermoscopic features (milia-like cysts, perifollicular depigmentation, and hypertrichosis), and as never described in spitzoid tumours. In the remaining 71.4% of pigmented ASTs, the clinical and dermoscopic presentation was nonspecific, as 14.3% of cases presented with dermoscopic features of compound naevi, while in 57.1% of cases, it was not possible to differentiate from MM (Fig. 3).

Finally, in our series, hypopigmented tumours included both amelanotic and pigmented ASTs. In particular, 50% of lesions showed the combination of glomerular vessel distribution in amelanotic areas of the lesion together with the cobblestone pattern in pigmented sections (Fig. 2b). Differential diagnosis with MM was impossible in the rest of the cases that manifested a polymorphous vascular pattern of serpentine and dotted vessels and atypical pigment network.

Conclusion

ASTs are cutaneous lesions that are difficult to recognize clinically. The results of our study on 99 cases and a long follow-up of > 6 years show no recurrence or distant metastases, confirming the good clinical outcome, even in the case of SLN positivity. From a diagnostic point of view, our series shows a typical dermoscopic picture regarding amelanotic ASTs with a glomerular vascular pattern throughout the lesion in the absence of other dermoscopic parameters, making the correct diagnosis possible. Conversely, the correct clinical dermoscopic diagnosis becomes difficult in pigmented ASTs.

What's already known about this topic?

- ASTs are regarded as an intermediate category distinguished from prototypical Spitz naevus by presenting ≥ 1 atypical features and often by an uncertain malignant potential.
- Owing to their rarity, little is known about the long-term clinical behaviour of ASTs, and only a few studies have investigated their specific clinical and dermatoscopic features.

What does this study add?

- Our study shows a typical dermoscopic picture for amelanotic ASTs, with a glomerular vascular pattern in the absence of other dermoscopic parameters, making the correct diagnosis possible.
- Our data, which reflect 16 years of follow-up time in a cohort of 99 patients, show a favourable prognosis with no event of distant metastasis or recurrence, even in cases with SLNB positivity.

Conflict of interest

Conflict of interest: the authors declare that they have no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Supplementary Data S1 Questionnaire.