Benign Melanocytoma
(Pigmented Epithelioid Melanocytoma, Epithelioid Blue Nevus)

16.1 Introduction

In 1996, Aidan Carney reported in more detail on a peculiar intensely pigmented melanocytic neoplasm associated with the syndrome that bears his name. Some of the lesions were in a combined form, i.e., associated with other types of nevi (Carney and Ferreiro 1996). Drs. Carney and Ferreiro christened this bizarre lesion as epithelioid blue nevus both for the similarity with common blue nevus and the presence of epithelioid cells. There were no local or visceral metastases, and they considered the lesions as benign.

As the authors predicted, the following years saw reports of sporadic cases of epithelioid blue nevus, unrelated to Carney complex (O'Grady et al. 1999).

In 2004, Zembowicz, Carney, and Mihm (Zembowicz et al. 2004) renamed epithelioid blue nevus as pigmented epithelioid melanocytoma and grouped these lesions together with another heavily pigmented lesion that had been termed animal-type melanoma. In their paper, both sporadic epithelioid blue nevus and those of Carney complex, which had not been linked to metastatic disease, and animal-type melanoma, which had resulted in metastases in some cases, were judged indistinguishable from each other from a histological point of view. They proposed the term melanocytoma as a noncommittal rubric beneath which they could group lesions outside a benign/malignant dichotomy. They held that histological examination could not distinguish the cases in which distant metastasis occurred from the benign ones.

For practical purposes, we still think it is useful to maintain a distinction between cases that have a uniformly benign outcome and those that pose a low but finite risk of distant metastasis. According to our own experience (and from data collected from the literature), the benign lesions are:

- Melanocytoma in the setting of Carney complex
- Combined melanocytoma
- Melanocytoma with maturation in blue nevus, Spitz nevus, or other forms of nevus

The main drawback of this classification is that melanocytoma associated with Carney complex (invariably benign, as patients with Carney complex are not reported as dying of metastatic melanoma, or at an increased risk for overt cutaneous melanoma developing in these lesions) and sporadic melanocytoma not associated with the complex are histologically very similar. Does the sole presence of the syndrome protect the patient from metastatic spread, or are these histologically identical melanocytoma benign, despite the reportedly high frequency of positive sentinel lymph node biopsy in this setting? In other words, is clinicopathological correlation a conditio sine qua non for the diagnosis of benign melanocytoma?

A second weakness of our classification is that the formal follow-up on our cases is limited. There is a reported case of a metastasis to the liver from a combined melanocytoma in an infant (though with an apparently favorable longer-term outcome). This particular lesion was illustrated in a previous paper (Richardson et al. 2002). Only a partial biopsy of a lesion that covered a third of the scalp was taken, and it showed sheets of epithelioid melanocytes. This appearance contrasts with that of the singly dispersed cells or cells in very small groups in the published photomicrographs in Carney's initial description of epithelioid blue nevus.

Zembowicz and Mihm published follow-up data on their series in 2009, showing that even though many of the patient had substantial lymph node deposits, more distant spread did not become manifested (Mandal et al. 2009).

With these considerations as a premise, we report in this chapter as "benign melanocytoma" the syndromic cases associated with Carney complex and the melanocytoma combined in any way with other types of nevi. Sporadic lesions resembling benign melanocytoma with unpredictable metastatic potential are reported in Chap. 39 as melanocytoma tout court.

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16.2 Clinical Features

Melanocytoma in Carney complex is reported as a domed, papular, or nodular (exophytic) lesion with variable features (Carney and Stratakis 1998). A melanoma is suspected quite frequently due to the dark blue or purple color of the lesion. Lesions are multiple in 45% of cases. Patients characteristically have other melanocytic lesions such as common blue nevus and lentigines. Familial occurrences are reportedly present in 36%. Patients are young with a mean age of 16 (3–39). In 71% of the cases reported in the main paper dealing with the subject, the lesions were associated or juxtaposed to another nevus or melanocytic abnormality.

Carney complex stigmata beyond melanocytomas are detailed in the box on this page.

As regards the other forms of melanocytoma that we illustrate in this chapter (i.e., combined melanocytoma not related to Carney complex and melanocytoma with extensive maturation in other type of nevi), we do not have much detailed clinical information. In the few cases in which we can obtain clinical details, the patient reports a long-standing lesion with a recent alteration of the color (Groben et al. 2000; Izquierdo et al. 2001; Ward 2006).

Carney complex

Carney complex patients have a combination of the following:

- Myxoma in the heart, skin and breast
- Multiple lentigines, blue nevi and melanocytoma
- Pigmented psammomatous schwannoma
- Endocrine overactivity caused by:
  - Nodular adrenal disease (Cushing disease)
  - Pituitary adenoma (acromegaly)
  - Sertoli cell tumor (sexual precocity)

Melanocytoma is present in 10% of the patients

16.3 Histological Features

16.3.1 Melanocytoma in Carney Complex

What is meant here as benign melanocytoma was described in Carney's seminal paper as epithelioid blue nevus, a term nowadays used for a variant of common blue nevus (see Chap. 10). The characteristics of melanocytoma associated with Carney complex (Figs. 16.1, 16.2, 16.3, and 16.4) are:

- Many cases have a wedge-shaped silhouette or a more rectangular profile. While the low cellularity results in indistinct margins when seen at high magnification, at scanning magnification, it seems quite well circumscribed.
- Epidermal hyperplasia, occasionally striking and reminiscent of that seen in Spitz nevus (hyperkeratosis, hypergranulosis, acanthosis), is seen in some cases. Rete ridges are elongated especially if a junctional component is present (which is mostly focused at the ridges); in some cases, however, the epidermis is normal or even attenuated.
- Junctional component is variable but rarely is conspicuous. Most of the compound forms are characterized by isolated junctional melanocytes. Most characteristically, the junctional component is represented by strikingly dendritic melanocytes. Dendrites extend throughout much of the spinous layer. A few cases, like that of Fig. 1 from Carney's paper (Carney and Ferreiro 1996) on epithelioid blue nevi, have large junctional nests outlined by clefts, resembling those of a Spitz nevus.
- Some melanocytomas are entirely intradermal, with a thin grenz zone separating the lesion from the epidermis; cases are reported with a deep extension reaching the subcutis.
- The tumor is darkly pigmented, melanin being present both in melanocytes and melanophages. The pigment is usually well distributed across the lesion, and occasionally a vertical gradient is seen.
- Cells in the dermis are usually in single units or very small groups, and no large well-formed nests are seen; there is little fibrosis.
- Four cell types have been described: elongated spindle cells with occasionally visible cytoplasmic dendrites, small epithelioid cells, large epithelioid cells, and melanophages. The large epithelioid ones can have a peculiar distribution of melanin at the periphery of the cytoplasm (a distribution which gives to the cell a fried egg-like appearance). Some papers have described melanophages as rare, but our surmise is that some of the descriptions of large globular cells with coarse pigment actually refer to melanophages and that these make up larger proportions of the lesions than several authors have wanted to admit.
- Cells do not show maturation (i.e., they do not decrease in size) as they go deeper in the dermis; mitoses are infrequent, but in one case, 3/mm^2 were noted.
- The epithelioid melanocytes have large pale nuclei with dispersed chromatin and a prominent nucleolus.

16.3.2 Combined Melanocytoma

In our own experience (Figs. 16.5 and 16.6), combined melanocytoma is within, beside, or beneath a common nevus (with some "congenital features"), although cases with a Spitz nevic component seem to occur as well. The two entities are quite distinct from each other: the melanocytoma component is darkly pigmented and composed of the characteristic combination of dendritic and epithelioid cells and melanophages. The epithelioid cells have a clear vesicular nucleus with prominent nucleolus. This component of the lesion is similar to melanocytoma in Carney complex as noted above. Mitoses in our cases have been very few.

The congenital nevus component is unremarkable. While many forms of combined nevi have areas with a transition, this particular combination does not.

16.3.3 Melanocytoma Maturing in Other Forms of Nevi

This form of melanocytoma is characterized by a bizonal pattern (Figs. 16.7, 16.8, 16.9, and 16.10). The melanocytoma features are on the top, whereas a more mature, innocent-looking nevus is beneath. The melanocytoma cells gradually blend with the nevus elements. The nevus in which melanocytoma evolves is usually a sort of sclerotic common blue nevus; sometimes, one sees the features of Spitz nevus or a bizarre combination of blue and Spitz nevi.

16.4 Differential Diagnosis

The melanocytoma associated with Carney complex is indistinguishable from its sporadic counterpart, which often shows involvement of lymph nodes (Chap. 39). Whether nodes are involved in Carney complex is unknown, as sentinel node biopsies are not done in that setting.

Combined melanocytoma is frequently confused with melanoma developing in a nevus. The two components of the neoplasm are so different from each other in cytological features and pigmentation that the misdiagnosis is indeed understandable. The correct assessment of a combined but benign melanocytoma can be made considering the heterogeneous combination of cellular component of the pigmented area: elongated dendritic cells are intermingled with epithelioid ones and melanophages (these features are rare in melanoma, with the exception of the animal type, if that really is an entity); moreover, the epidermis is usually symmetrically hyperplastic in the involved area and there is no pagetoid spread above the junction. Mitoses are almost undetectable. Moreover, the pigmented areas do not compress nor destroy the associated common or superficial congenital nevus.

Regarding the one case of combined melanocytoma reported as metastatic to the liver, we do not know the meaning of this yet. As noted above, its appearance was quite different, with sheets of cells.

In regard to the benign melanocytoma characterized by maturation in its deeper portion, the differential diagnosis is solved by the benign-looking cytology of the nevus cells in the "mature" zone deep in the dermis. Here, the lesion has the features of a blue nevus, Spitz nevus, or a combination of both. Moreover, these benign-looking cells are occasionally embedded in mature or even keloidal collagen fibers. These features, along with a complete mitotic quiescence, rule out melanoma.

Most probably future genomic assessment of these lesions will contribute to their correct and reproducible classification (Battistella et al. 2010).

16.5 Further Reading

Battistella M, Prochazkova-Carlotti M, Berrebi D et al (2010) Two congenital cases of pigmented epithelioid melanocytoma studied by fluorescent in situ hybridization for melanocytic tumors: case reports and review of these recent topics. Dermatology 221(2):97–106

Carney JA, Ferreiro JA (1996) The epithelioid blue nevus A multicentric familial tumor with important associations, including cardiac myxoma and psammomatous melanotic schwannoma. Am J Surg Pathol 20(3):259–272

Carney JA, Stratakis CA (1998) Epithelioid blue nevus and psammomatous melanotic schwannoma: the unusual pigmented skin tumors of the Carney complex. Semin Diagn Pathol 15(3):216–224

Groben PA, Harvell JD, White WL (2000) Epithelioid blue nevus: neoplasm Sui generis or variation on a theme? Am J Dermatopathol 22(6):473–488

Izquierdo MJ, Pastor MA, Carrasco L et al (2001) Epithelioid blue naevus of the genital mucosa: report of four cases. Br J Dermatol 145(3):496–501

Mandal RV, Murali R, Lundquist KF (2009) Pigmented epithelioid melanocytoma: favorable outcome after 5-year follow-up. Am J Surg Pathol 33(12):1778–1782

O'Grady TC, Barr RJ, Billman G et al (1999) Epithelioid blue nevus occurring in children with no evidence of Carney complex. Am J Dermatopathol 21(5):483–486

Richardson SK, Tannous ZS, Mihm MC Jr (2002) Congenital and infantile melanoma: review of the literature and report of an uncommon variant, pigment-synthesizing melanoma. J Am Acad Dermatol 2002 47(1):77–90

Ward JR, Brady SP, Tada H et al (2006) Pigmented epithelioid melanocytoma. Int J Dermatol 45(12):1403–1405

Zembowicz A, Carney JA, Mihm MC (2004) Pigmented epithelioid melanocytoma: a low-grade melanocytic tumor with metastatic potential indistinguishable from animal-type melanoma and epithelioid blue nevus. Am J Surg Pathol 28(1):31–40

16.6 Summary

- What is now called melanocytoma (pigmented epithelioid melanocytoma) was previously labeled epithelioid blue nevus, a subset of blue nevus associated with Carney complex. Soon sporadic forms were reported as well.
- Other authors consider melanocytoma correlated with animal-type melanoma and clinically unpredictable.
- We propose here to divide melanocytoma in benign and potentially metastatic forms.
- Forms that we consider benign are:
  - Melanocytoma in the setting of Carney complex
  - Combined melanocytoma
  - Melanocytoma with maturation in blue nevus, Spitz nevus, or other forms of nevus
- Forms that we consider potentially metastatic to local nodes are the sporadic ones not combined with other nevi.

Fig. 16.1
Benign melanocytoma in Carney complex

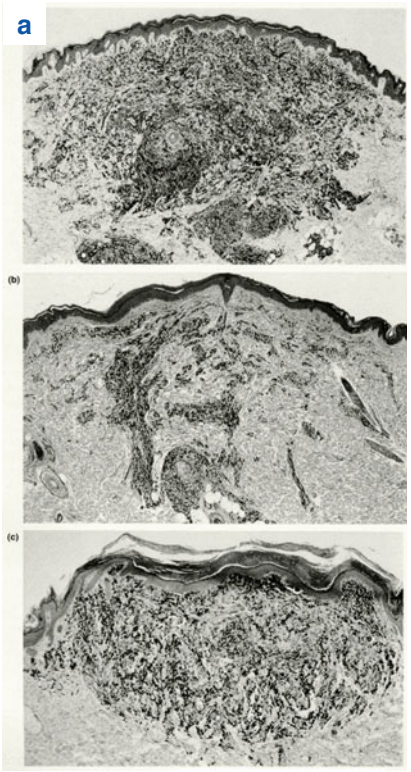
These are among the figures illustrating the original cases reported by Aidan Carney and Jorge Ferreiro in their 1996 paper on epithelioid blue nevus.

*The architectural features are somewhat variable (**a**): in the pictures at the top and bottom of this page, there is a vaguely wedge-shaped silhouette. A plexiform pattern reminiscent of a blue nevus or deep penetrating nevus is present in the middle picture.*

*The hallmarks of the epithelioid blue nevi/melanocytomas depicted by Carney include the combination of cells depicted in figure (**b**):*
- Elongated spindle and dendritic melanocytes full of melanin.
- Small epithelioid cells with vesicular nucleus and a prominent nucleolus.
- a number of larger epithelioid cells with the same features as the small ones but more atypical and less pigmented; rare mitoses can be found (arrow).
- Melanophages.

These features are found also in the form of sporadic melanocytoma, irrespective of their metastatic potential

(From the American Journal of Surgical Pathology, with permission)



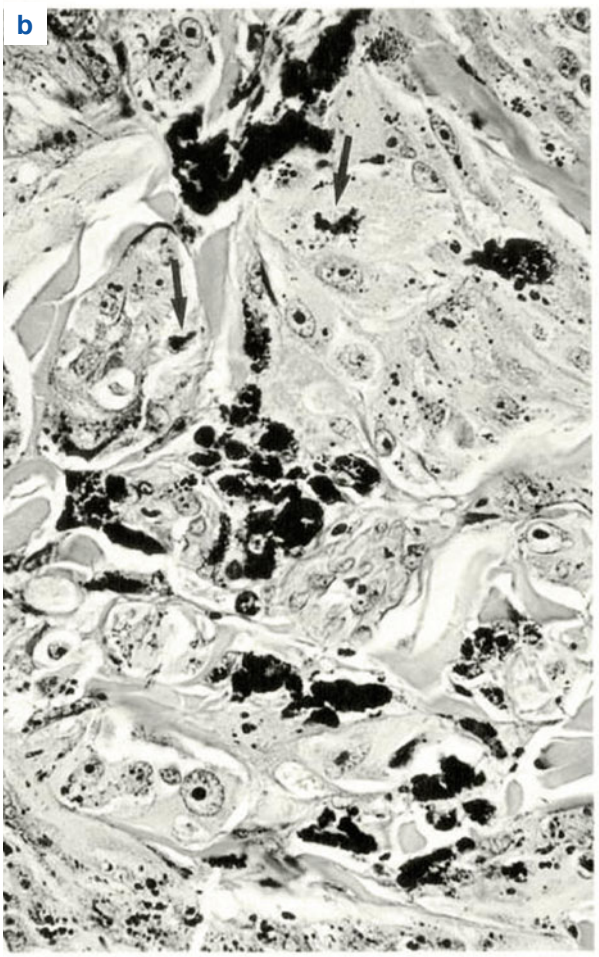


Fig. 16.2
Benign melanocytoma (in combined nevus) in Carney complex

*In this case, courtesy of Dr. Aidan Carney, a mushroom-shaped lesion (**a**) shows striking internal asymmetry.*

*On the left side there are plenty of melanophages (**b**) and large, oval to fusiform melanocytes with strikingly atypical, vesicular nuclei containing large and sometimes multiple nucleoli (**c**).*

The effect of cross-sectioning in different planes may exaggerate the degree of nuclear pleomorphism. The smaller nuclei may just be en face sections of larger ones.

The limited number of melanocytes coupled with their aberrant-appearing nuclei suggests an alteration in which cells have an aberrant genome but one with limited replicative potential

On the right side of the lesion a intradermal common nevus is seen (so the lesion can also be labelled as a combined nevus)

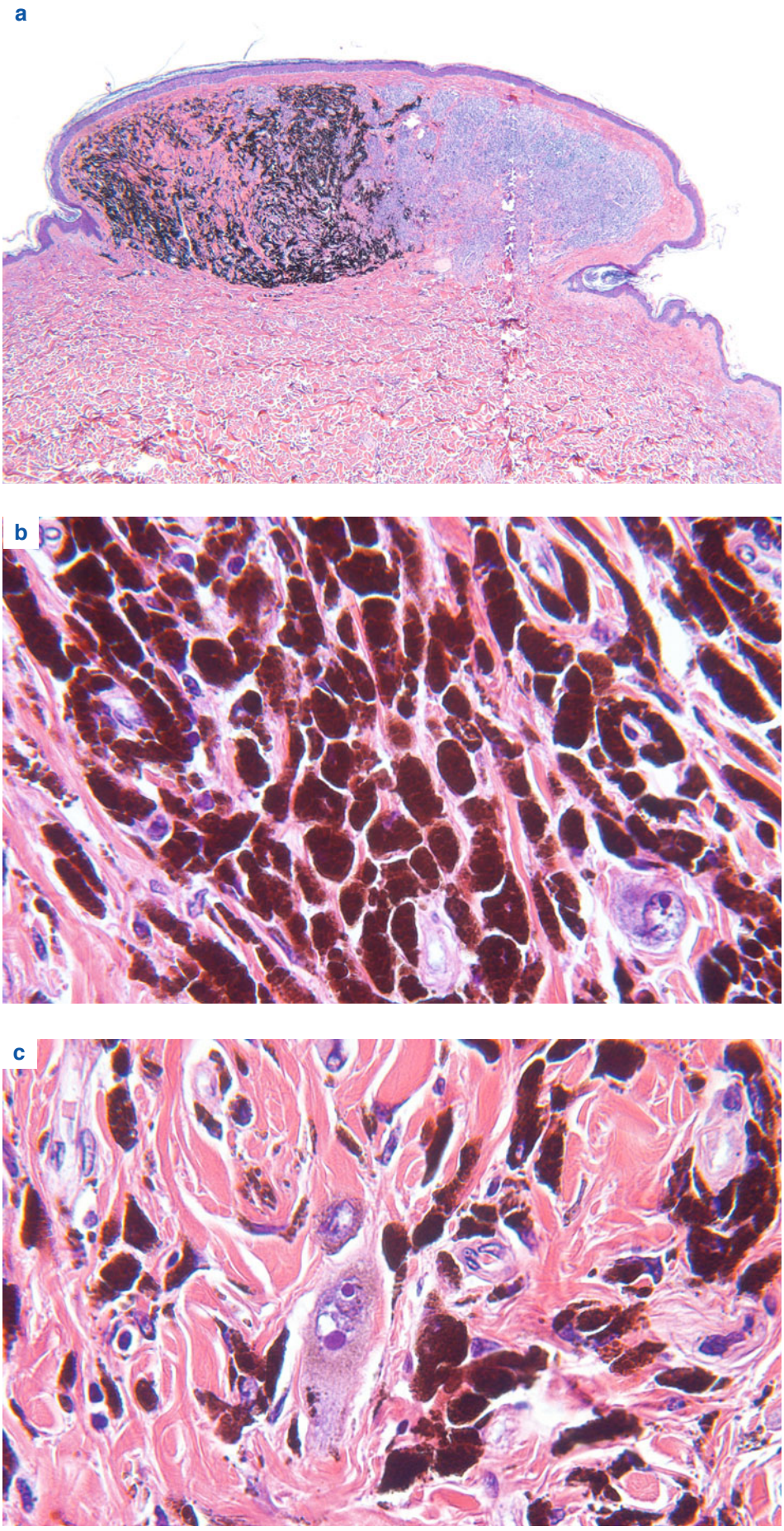


Fig. 16.3
Benign melanocytoma in Carney complex

*This lesion has a domed surface and wedged base (**a**), more similar to the silhouettes seen in the top and bottom pictures in Fig. 16.1a.*

*The composition of large, pleomorphic melanocytes, outnumbered by melanophages (**b**), is similar to that seen in Fig. 16.2.*

*While there are some features in common with those of common blue nevus, fibrosis is typically present in such lesions and is uncharacteristic of melanocytomas (**c**)*

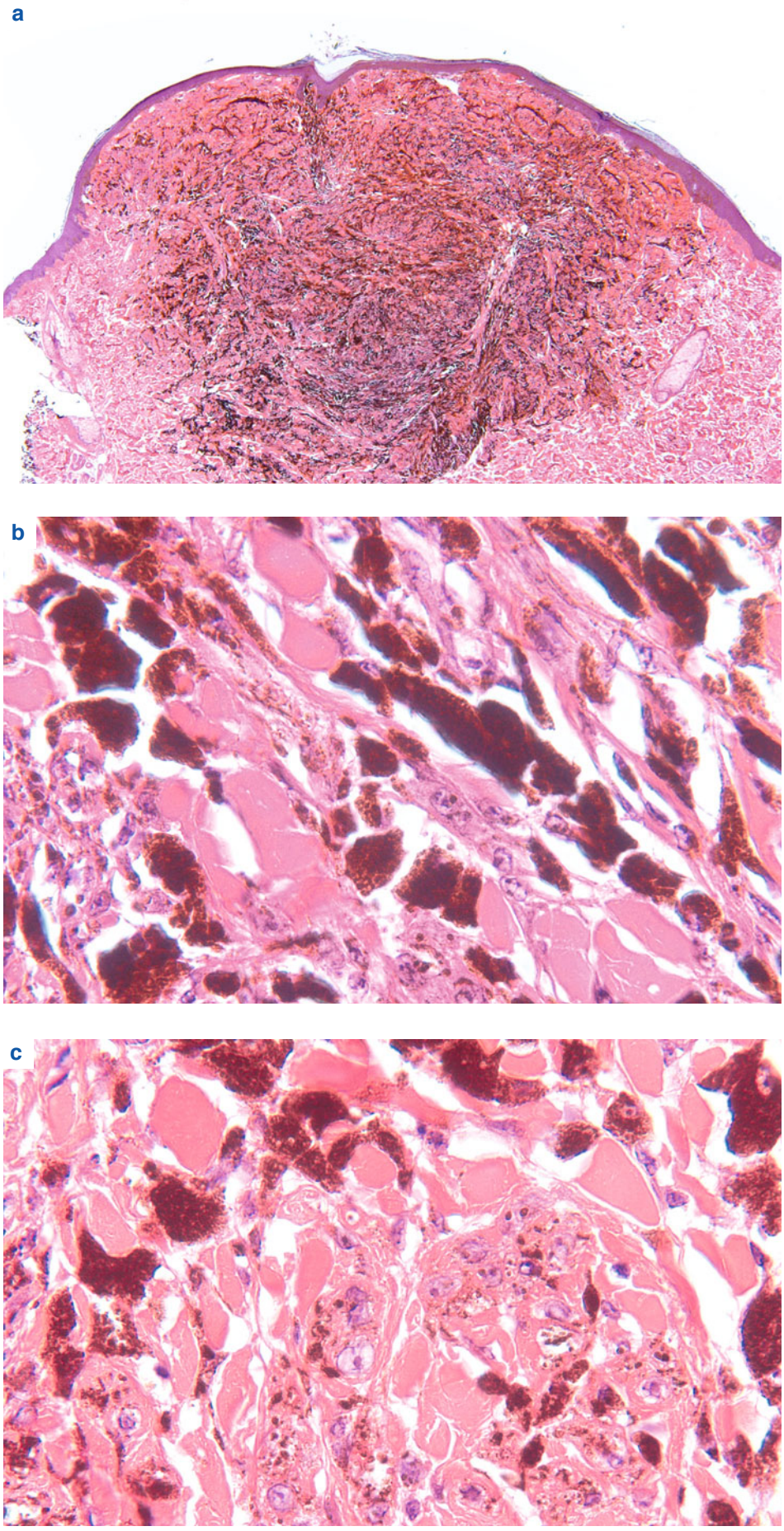


Fig. 16.4
Benign melanocytoma in Carney complex

*This lesion has a flatter surface (**a**), with melanophages again outnumbering melanocytes (**b**). The latter are arranged singly, rather than in nests or expansile-appearing collections. The average size of the melanocytes and of their nuclei is considerably smaller than in the preceding figures (**c**)*

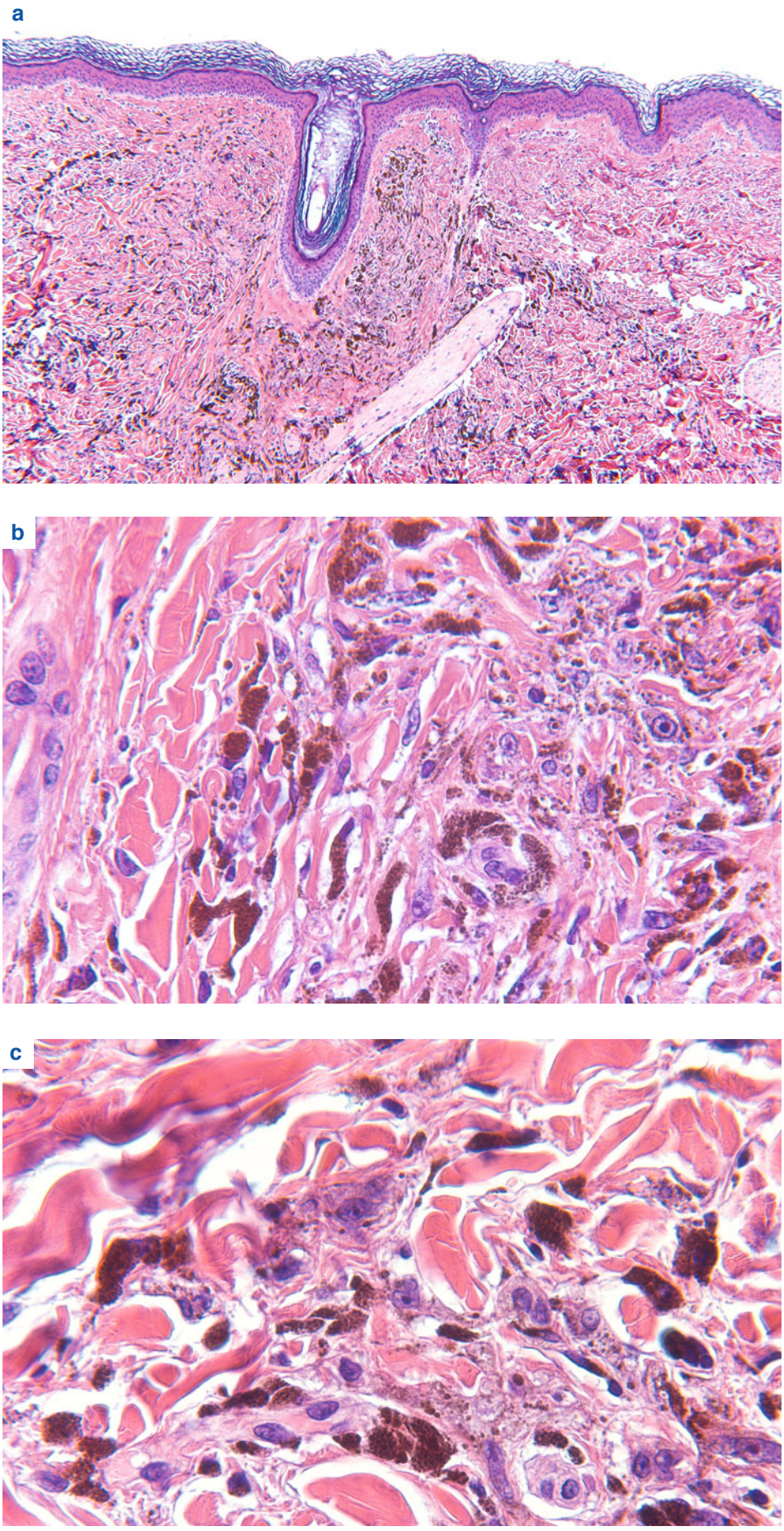


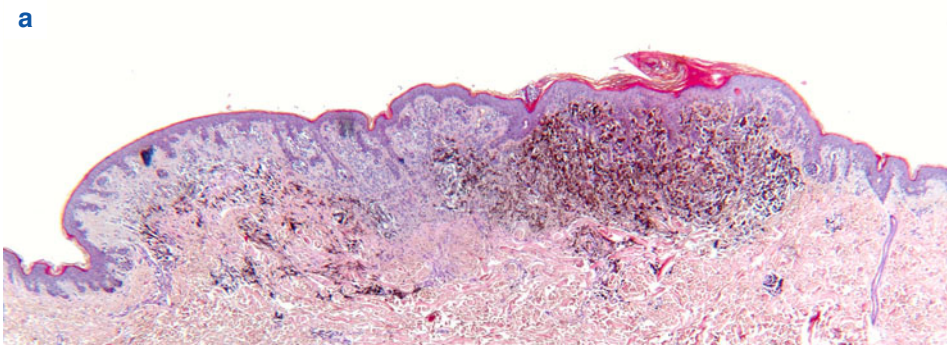
Fig. 16.5
Combined nevus with a melanocytomatous component

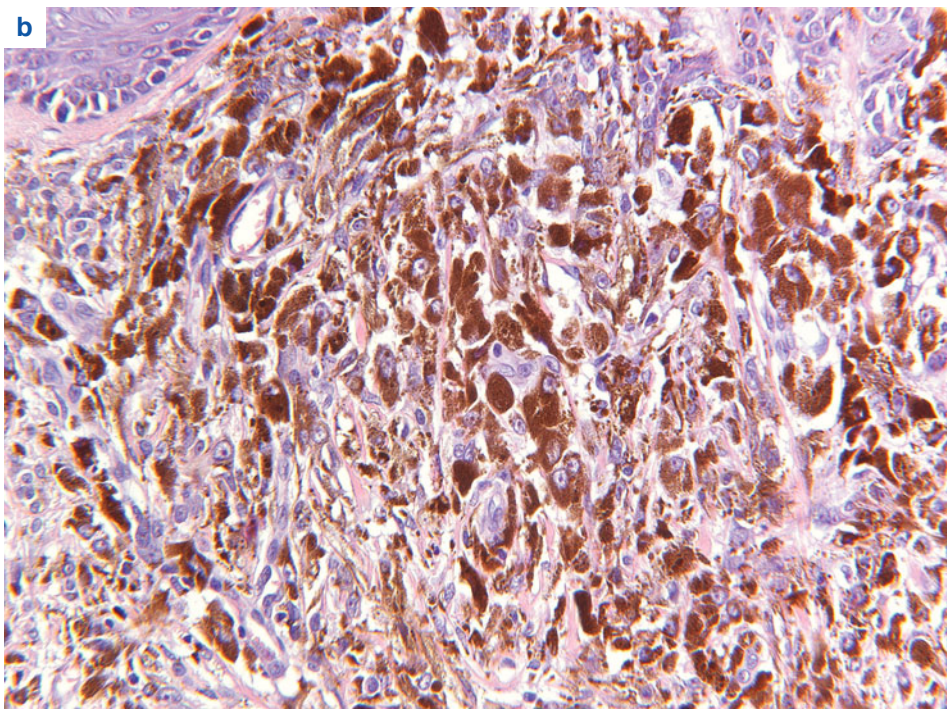
*The lesion illustrated here has two clear-cut, spatially separate components (**a**). On the left is a compound nevus with lightly pigmented cells, while on the right a darkly pigmented lesion occupies the field.*

*At high magnification (**b**, **c**), the pigmented component shows features consonant with a melanocytoma:*
- The silhouette of this component is wedge shaped.
- The epidermis above the lesion is irregularly hyperplastic, as is the case when the cells of a melanocytoma abut its undersurface; despite the resemblance to the epidermal changes that overlie Spitz nevi, Kamino bodies are not present, and if there is hyperkeratosis, it tends to be lamellar rather than compact.
- Melanocytes are mostly dendritic, but small epithelioid elements are present as well.
- Plenty of melanophages are present throughout the lesion.

Note the epidermal hyperplasia symmetrically tapering toward the border of the melanocytoma portion of this combined nevus.

Large atypical elements are not seen, nor are there mitotic figures





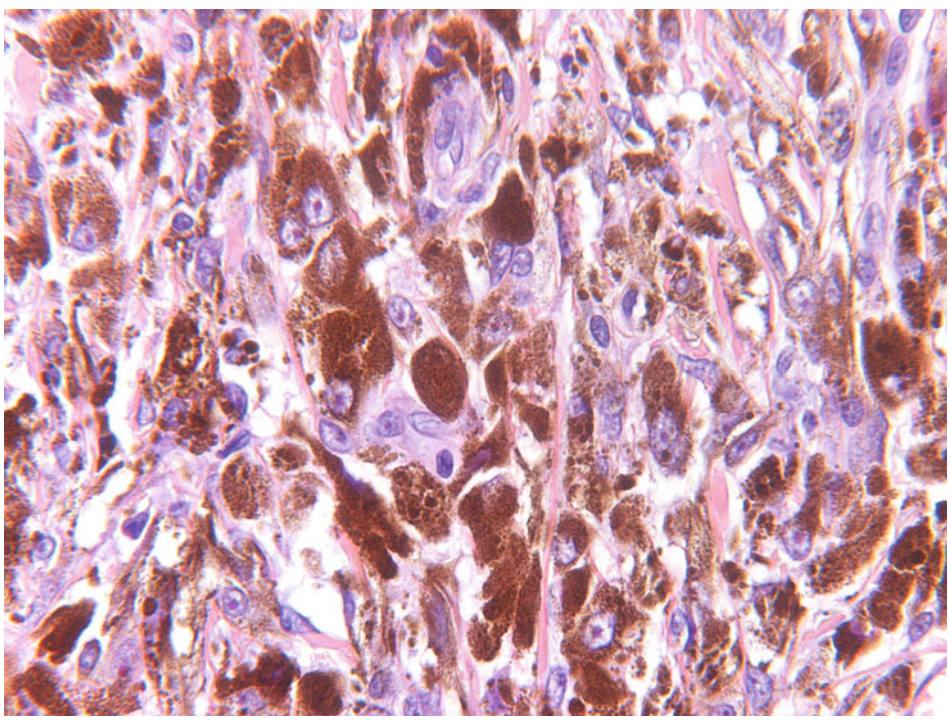
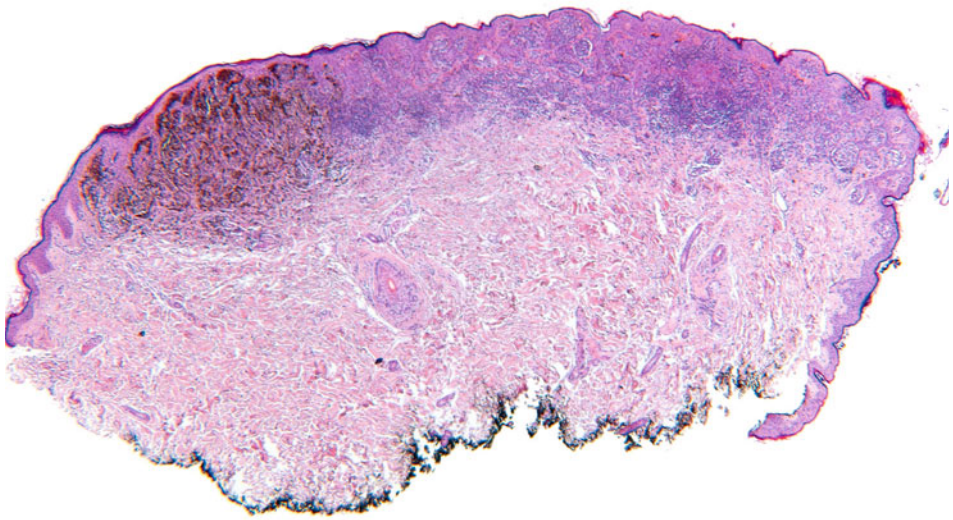


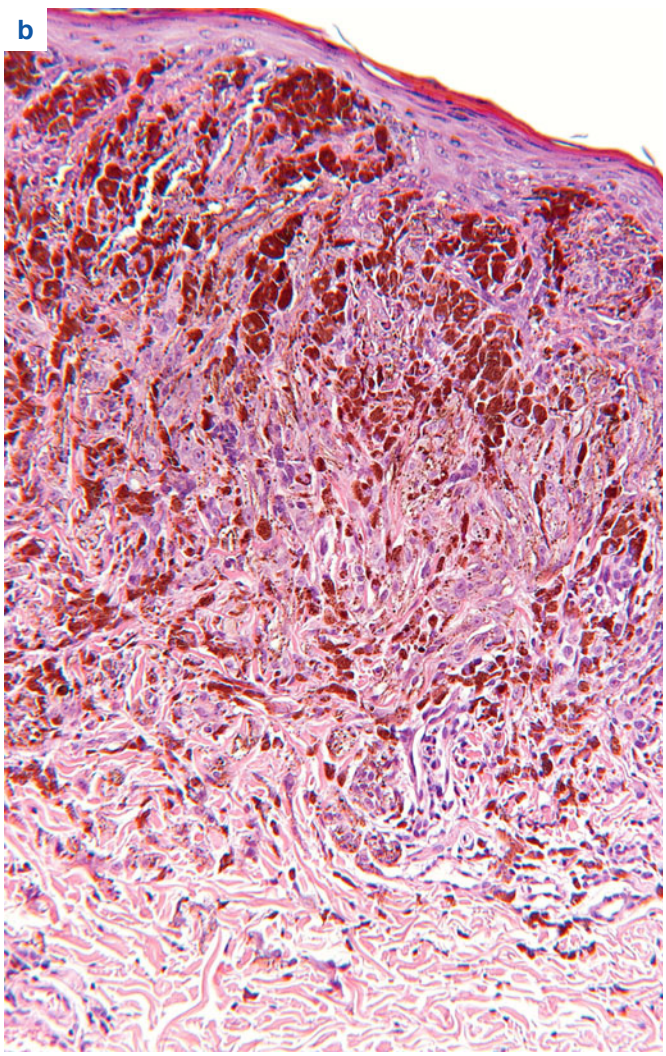
Fig. 16.6
Combined nevus with a melanocytomatous component

*This is a so-called side-by-side combined nevus (**a**). On the right is a compound nevus, on the left a hyperpigmented neoplasm.*

*At higher magnification, the features of melanocytoma are present in the latter area: abundant melanophages (**b**), large fusiform cells with large, vesicular nuclei (**c**), and dendritic processes. In our experience, many lesions have a predominance of one type of melanocytes and are accompanied by many melanophages.*

The patient was 7 years old





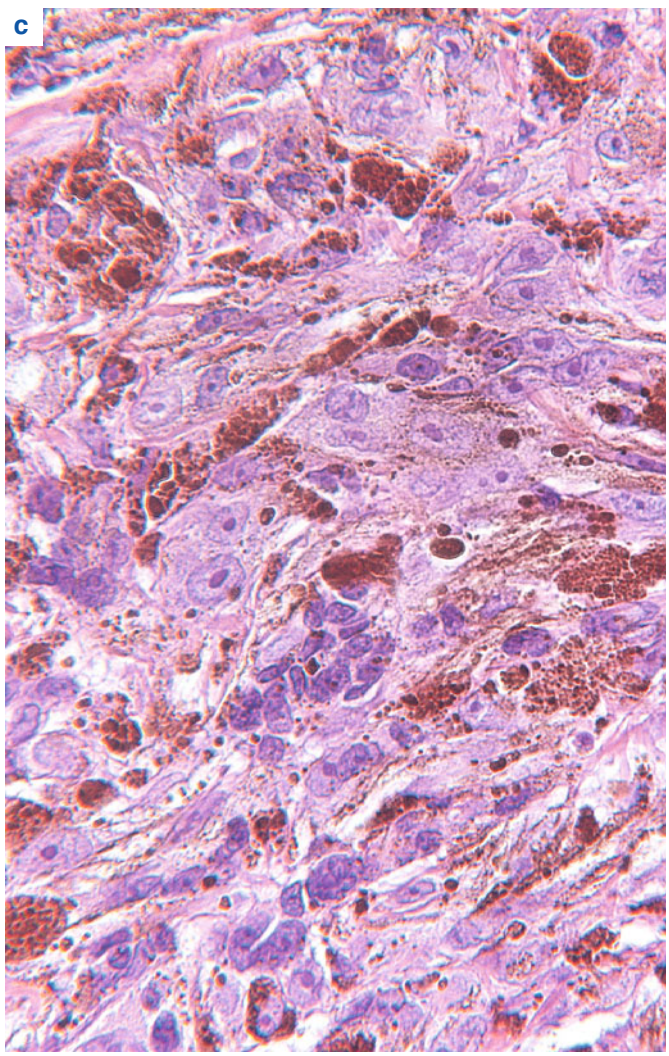
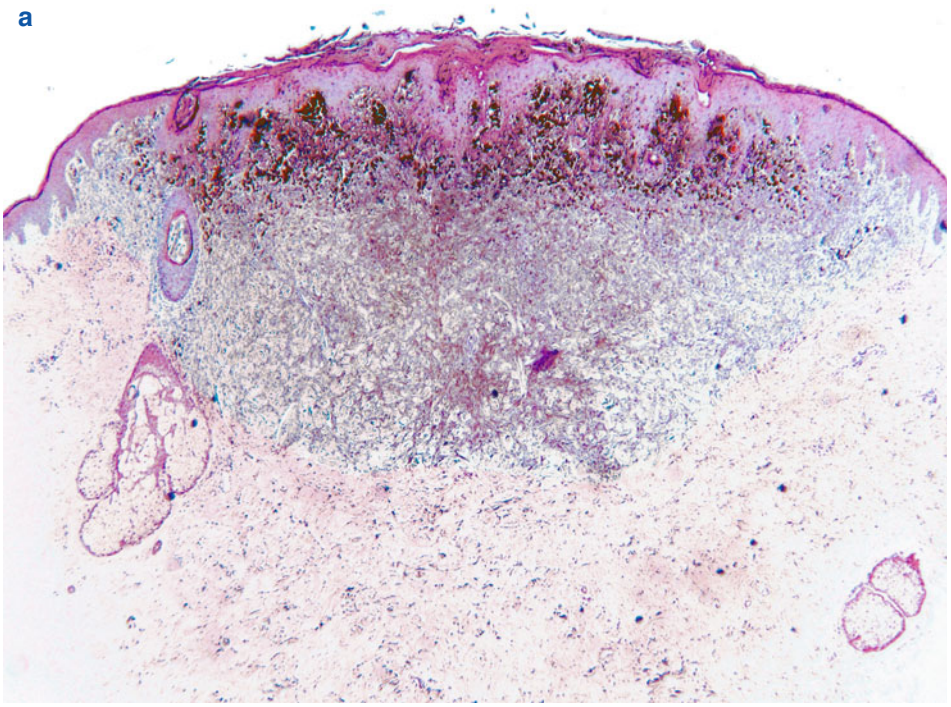
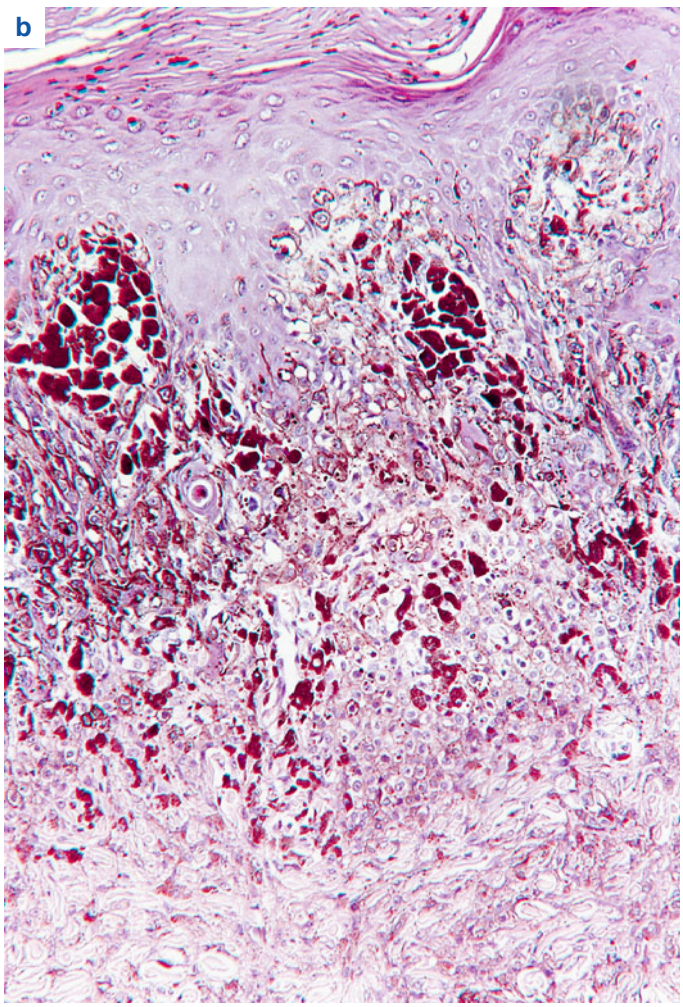
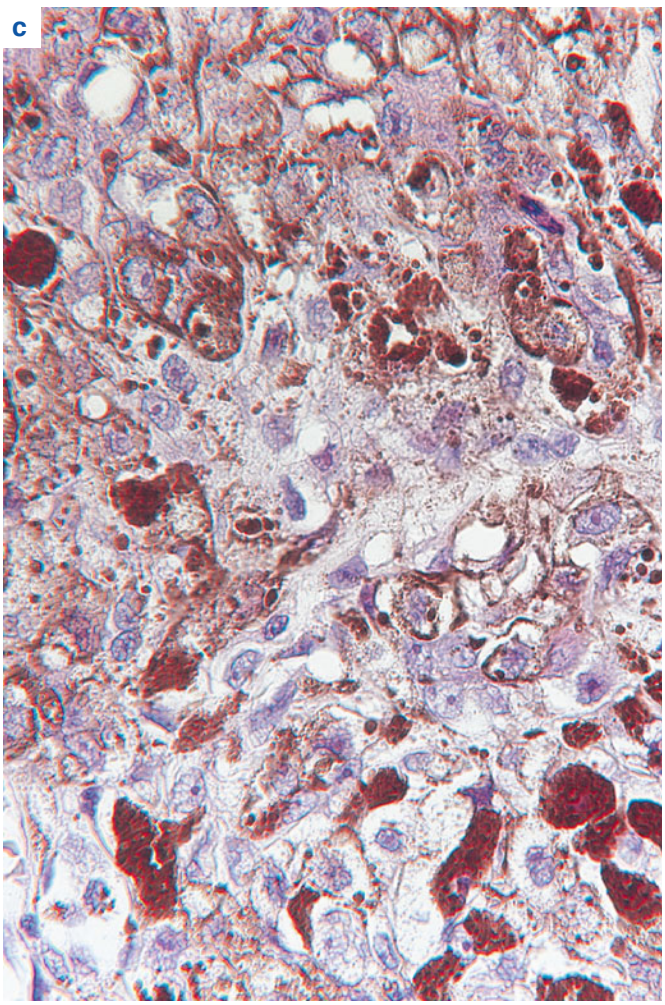


Fig. 16.7
Benign melanocytoma with features of maturation, and admixed common blue nevus

*There are at least three components in this distinctive melanocytic neoplasm (**a**). The melanocytoma is on the top (**b**, **c**), and the other populations lie beneath it. The upper part of the lesion has indeed the following features:*
- Epidermal hyperplasia with jagged ridges and hyperkeratosis
- Large epithelioid melanocytes with variably pigmented, pale cytoplasm
- Many melanophages, especially in dermal papillae
- A few small dendritic melanocytes







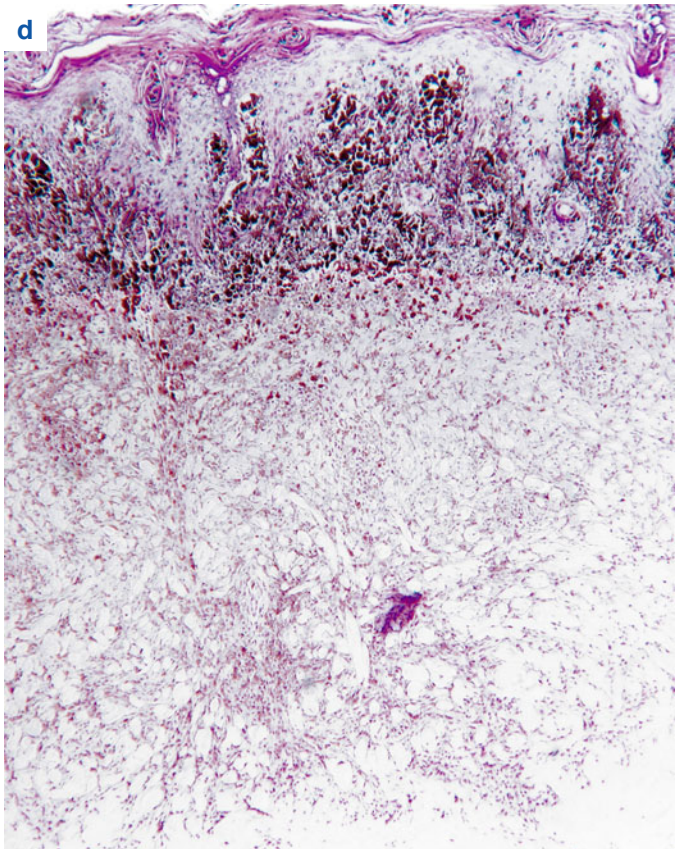
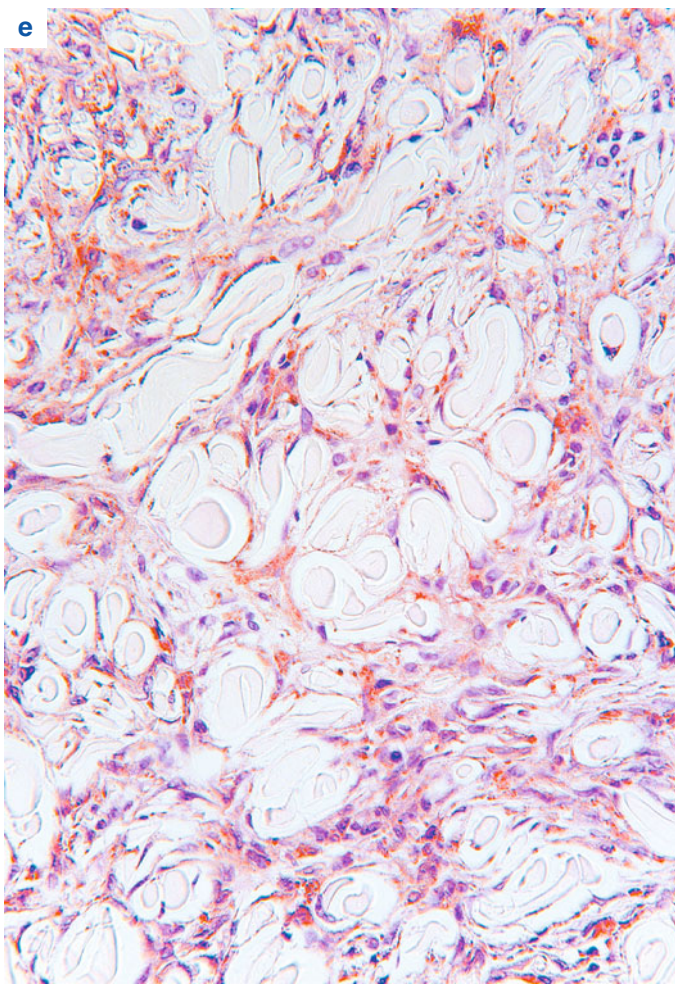


Fig. 16.7 (cont'd)
Benign melanocytoma with features of maturation, and admixed common blue nevus

*All these are features seen in melanocytoma. The epidermal hyperplasia (**d**) is more like that of a Spitz nevus and would be unheard of in any form of the blue nevus family of lesions, except for melanocytoma.*

*The predominant population in the lower part of the lesion resembles that of a common (Jadassohn-Tièche) form of blue nevus (**e**, **f**).*

The patient was 26 years old



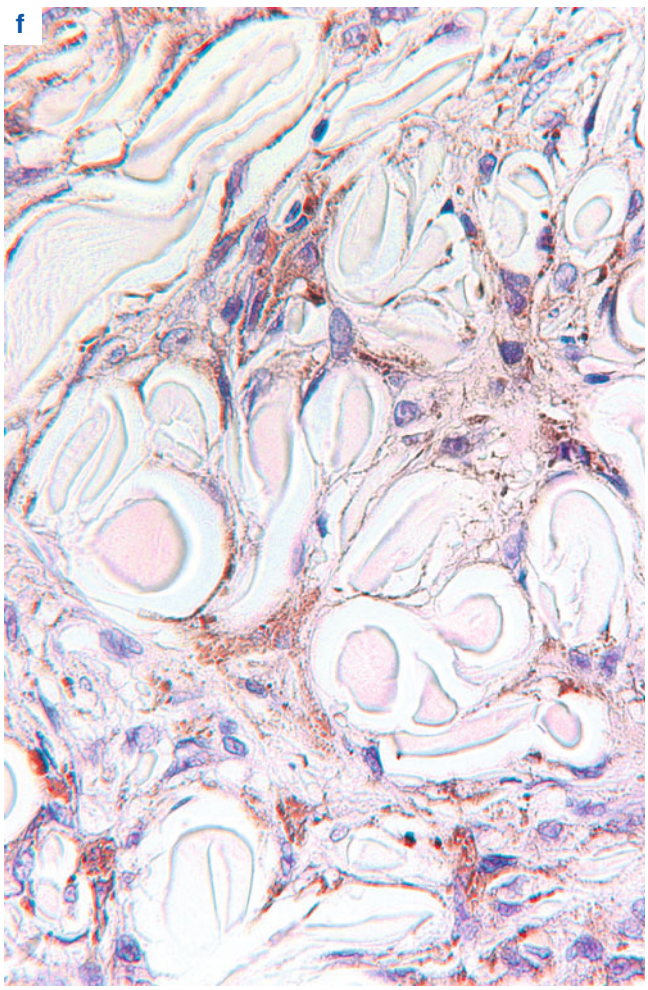
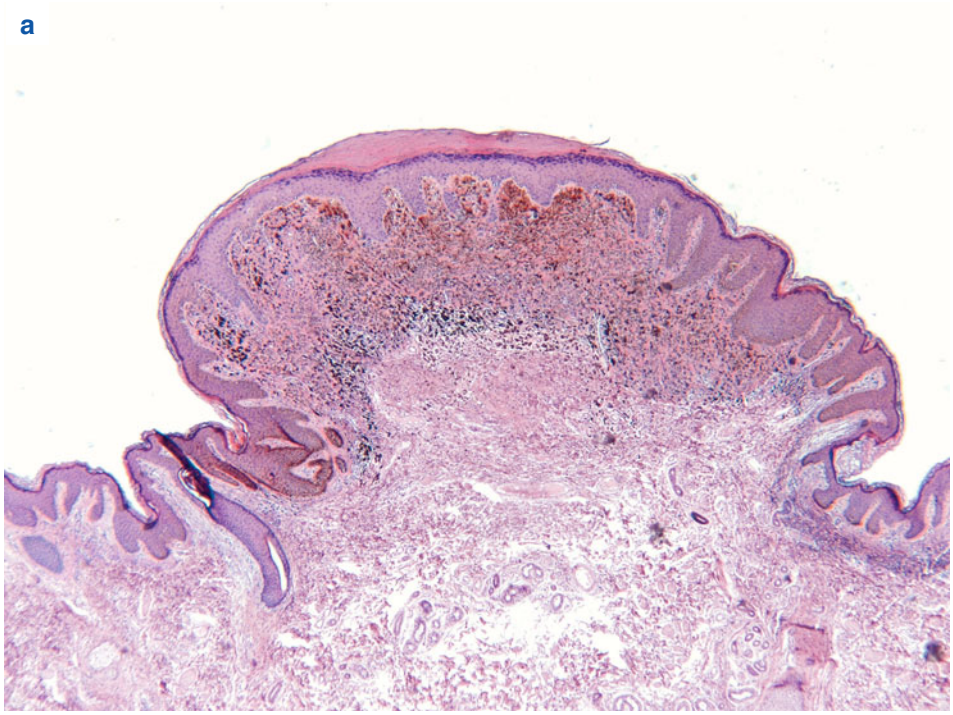
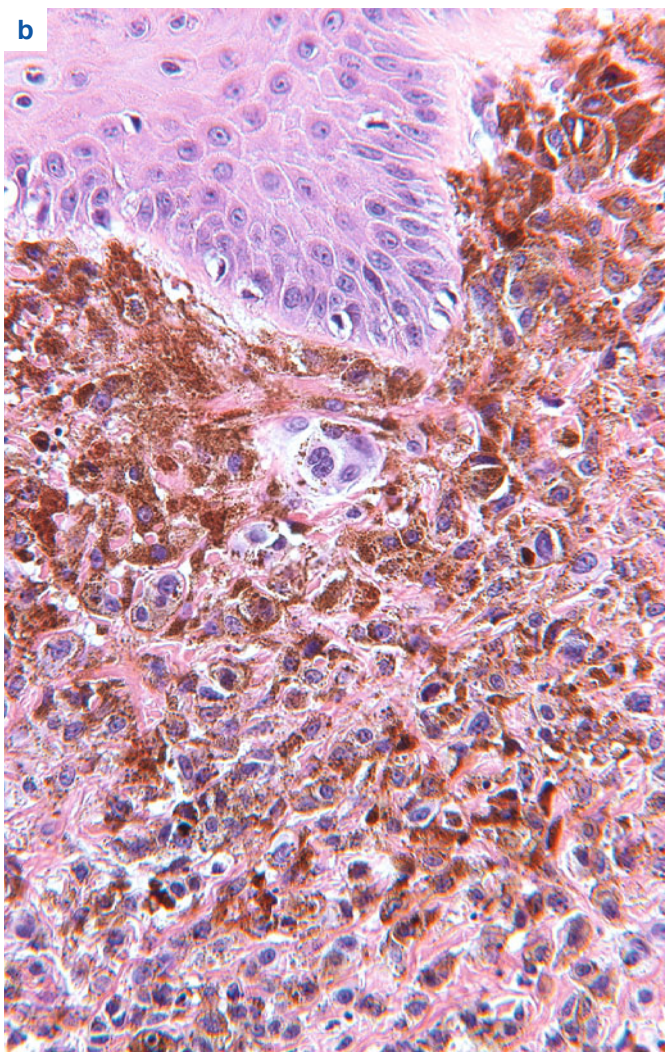
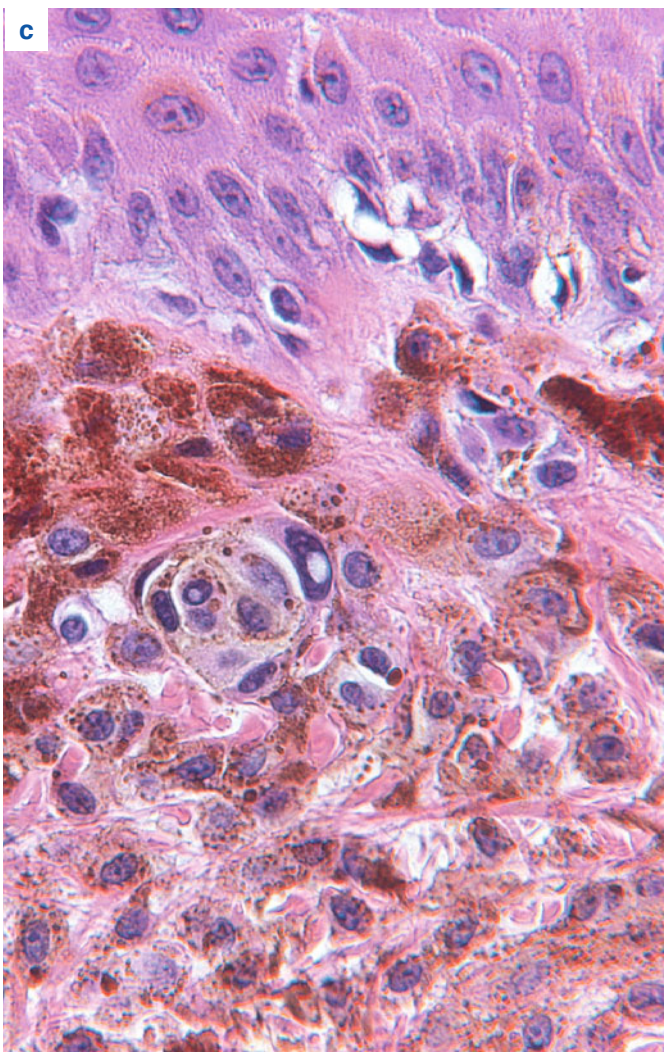


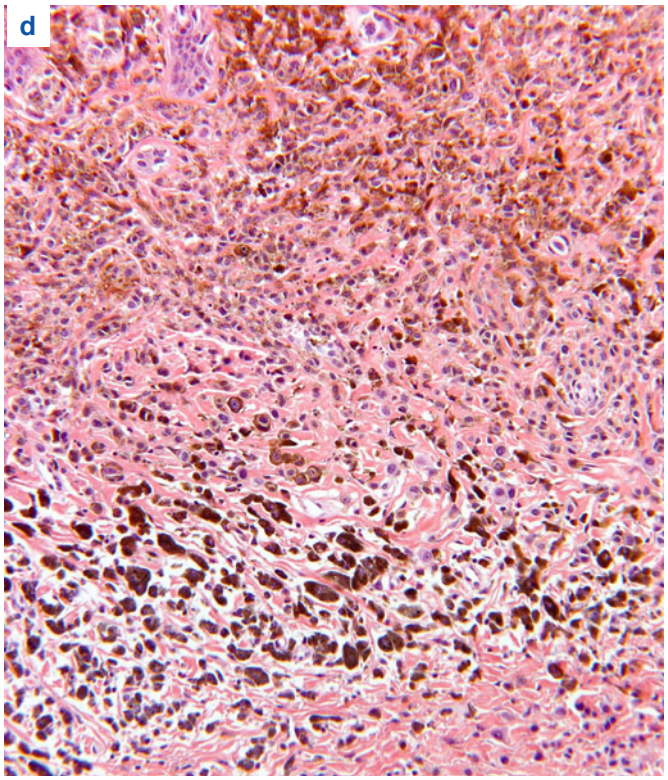
Fig. 16.8
Benign melanocytoma with maturation

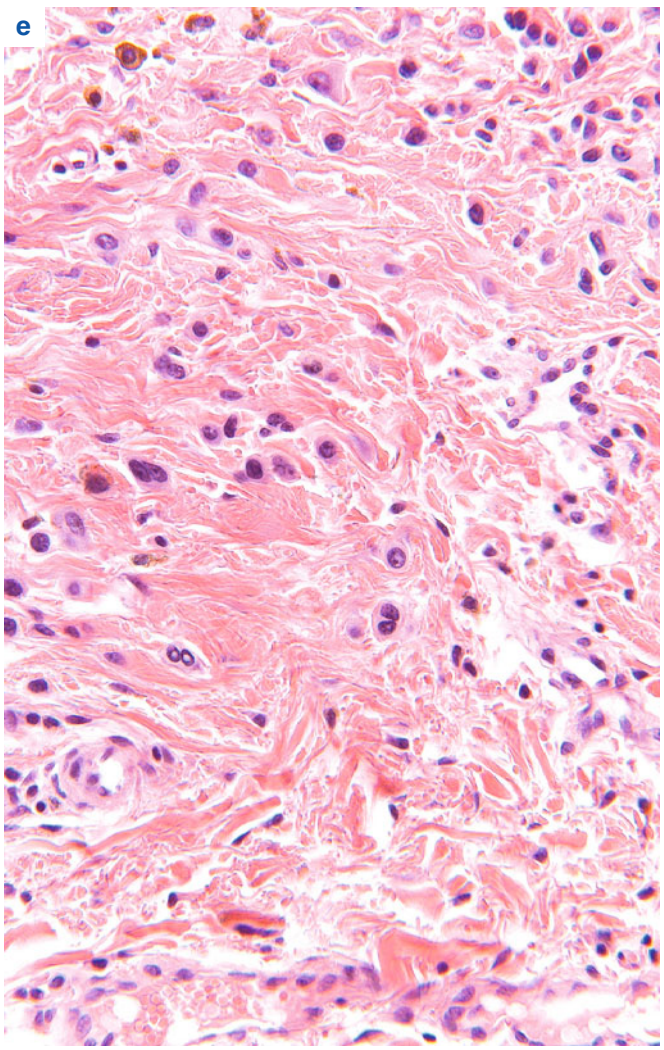
*One can apply generic criteria to this lesion and conclude it is a nevus. It is well circumscribed (**a**), its cellularity diminishes toward its base in an even fashion, and its cells mature cytologically. A few more distinctive findings mark it as a melanocytoma:*
*- There are large, epithelioid melanocytes with vesicular nuclei containing large nucleoli (**b**, **c**).*
*- Some cells have a peculiar distribution of melanin around the nucleus (**d**, **e**) and at the periphery of the cytoplasm ("fried egg" cells).*
- The lesional epidermis has the characteristic symmetrical hyperplasia frequently found in melanocytoma











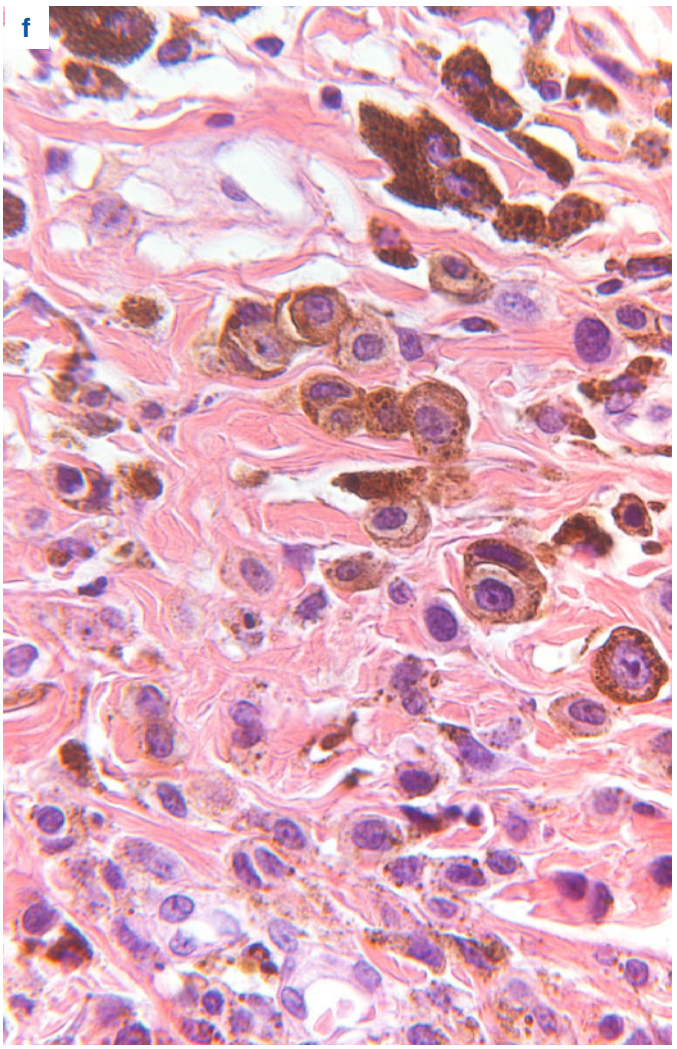


Fig. 16.8 (cont'd)
Benign melanocytoma with maturation

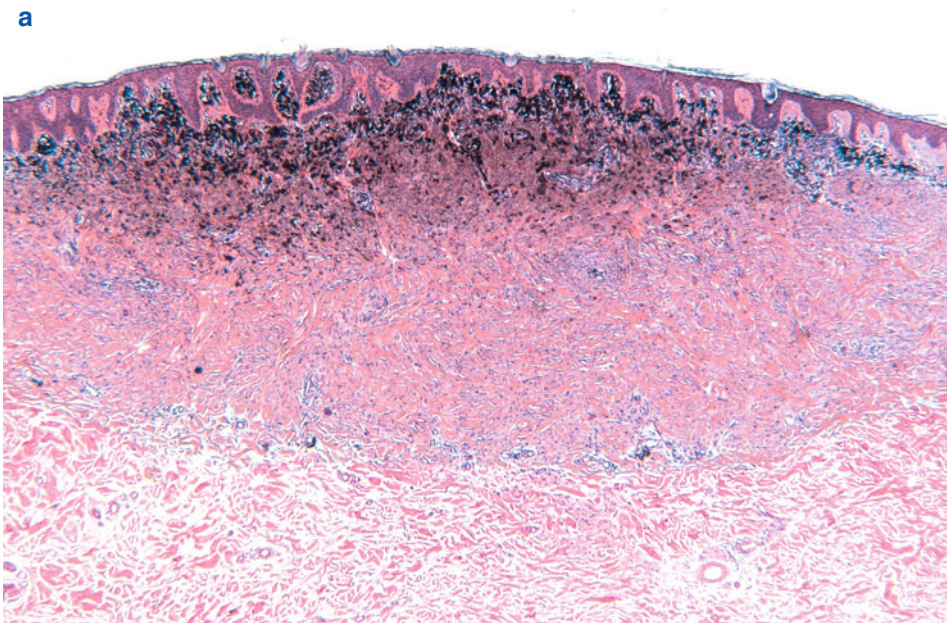
*Note that the bottom portion of the lesion is entirely composed of more mature-looking melanocytes. These cells are evenly dispersed between the native collagen fibers of the reticular dermis, with some fibrillar stroma (**f**).*

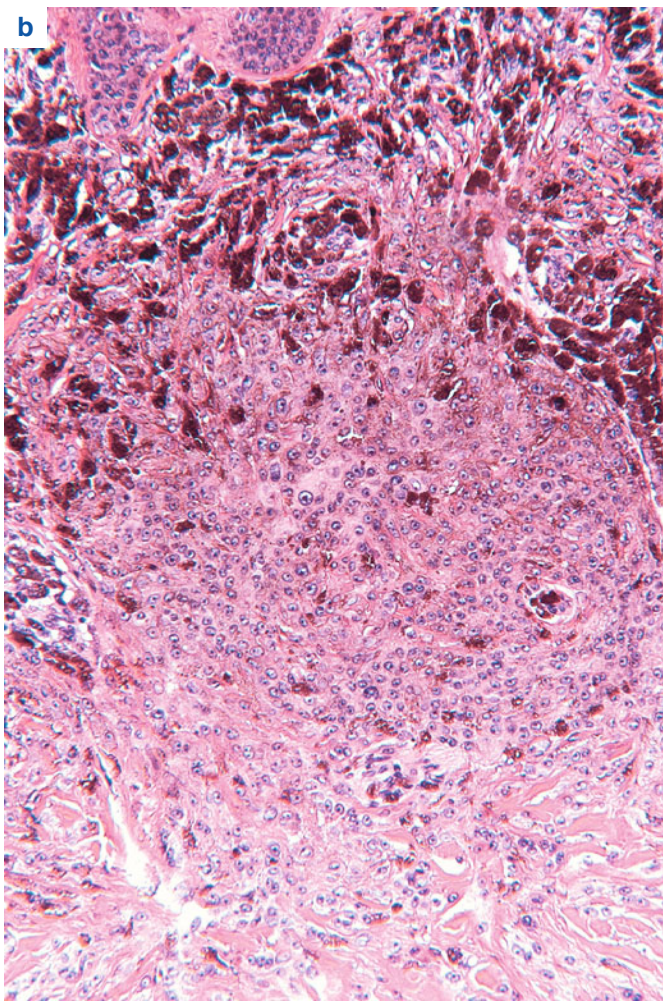
We failed to find a single mitosis in this section

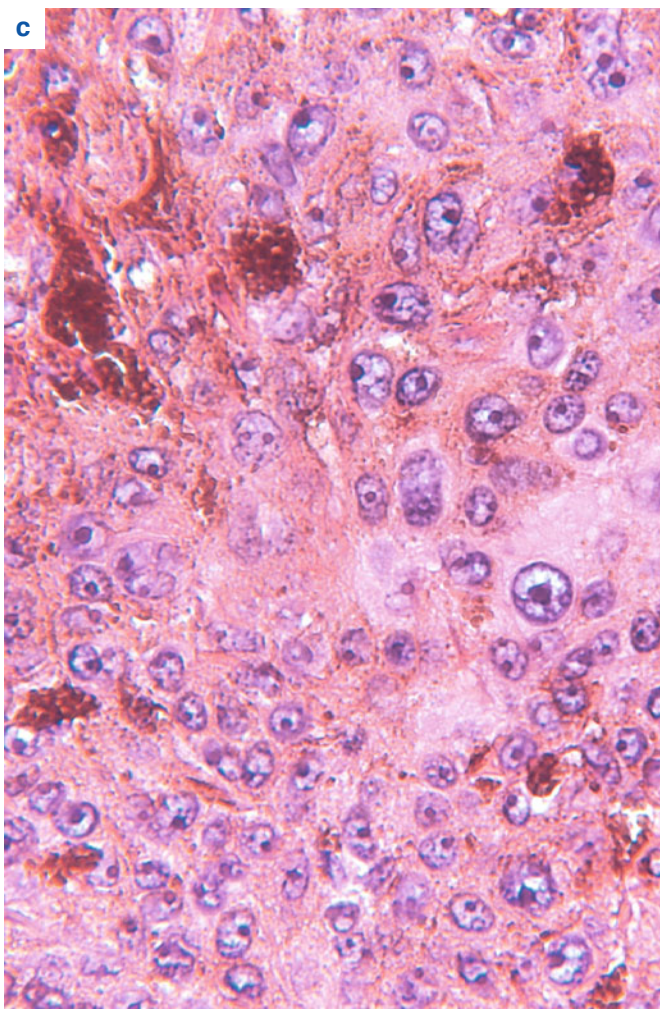
Fig. 16.9
Benign melanocytoma with maturation

*This nevus was sited on the abdomen of a 42-year-old female. The neoplasm is characterized by a symmetrical epidermal hyperplasia which is accentuated in its center and tapers at the edges of the lesion (**a**). Underneath the dome of the epidermis is a sort of pigmented umbrella.*

This combination is an indication that the nevus could be a melanocytoma. Similar features are seen in some Spitz and Reed nevi, in some examples of deeply pigmented conventional melanoma centered around follicles (some reported also as animal-type melanoma), and in some acral melanomas







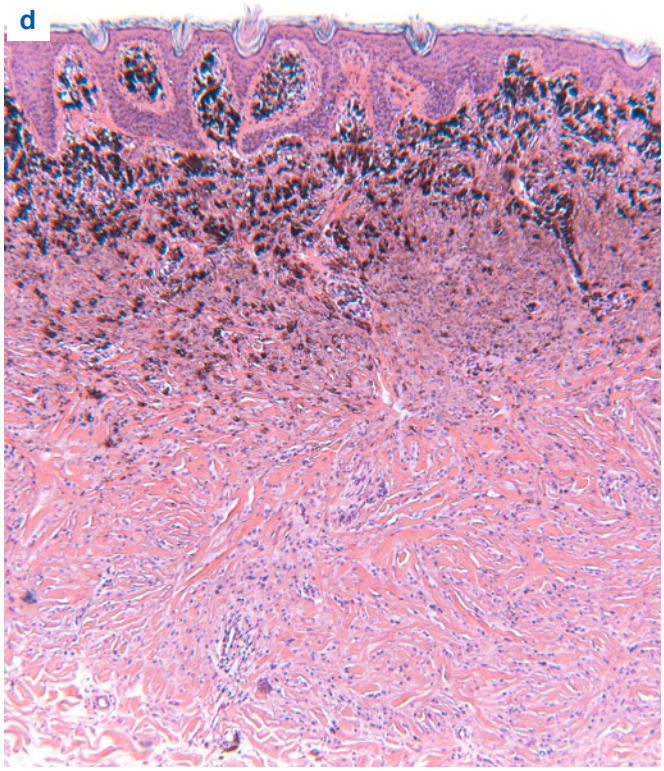
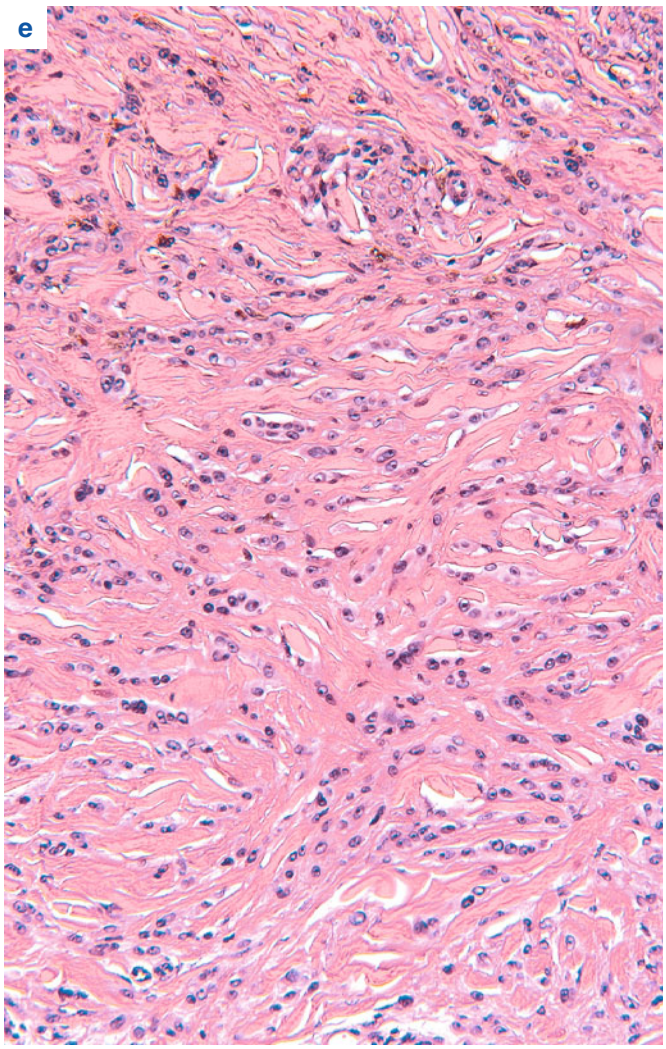


Fig. 16.9 (cont'd)
Benign melanocytoma with maturation

*At the top of the lesion, the melanocytes are epithelioid with vesicular nuclei and prominent nucleoli (**b**, **c**). These melanocytes are outnumbered by melanophages just beneath the epidermis (**d**).*
*The lowermost part of the nevus has the features we find in desmoplastic Spitz nevus, considering size and shape of the cells (**e**, **f**). As noted above, desmoplastic stroma is not depicted in the epithelioid nevi in Carney complex.*
Complete mitotic quiescence and strict monomorphism in the different horizontal planes of the neoplasm are all indications that the lesion is benign



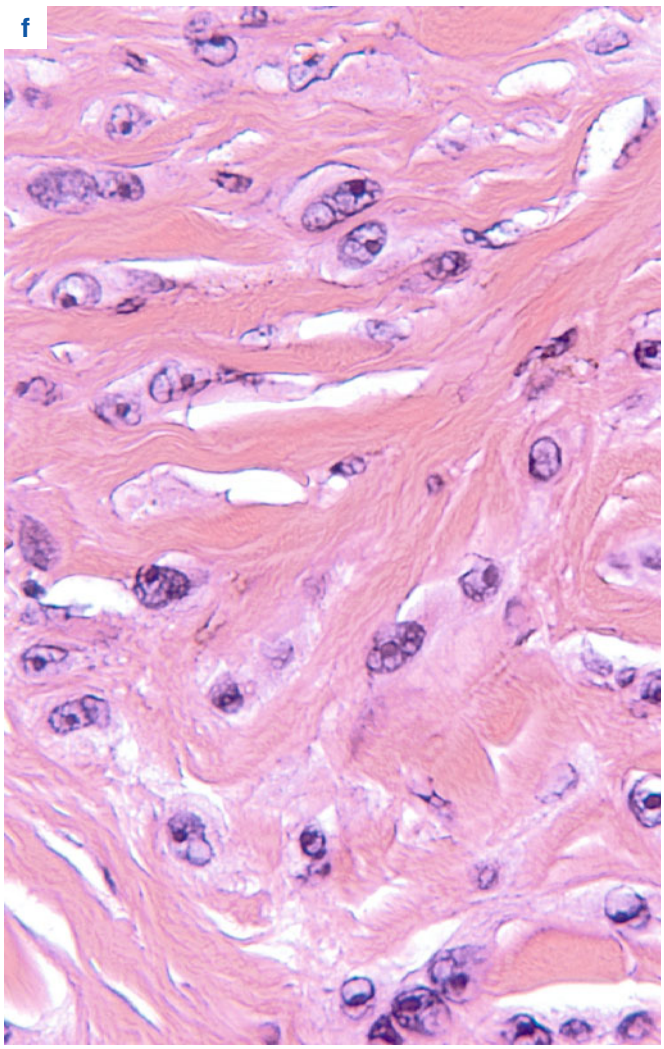


Fig. 16.10
Benign melanocytoma with maturation

*This nevus could just be labeled as a combined nevus (**a**). At the top, there are features of a melanocytoma (**b**), whereas at the bottom, there is a desmoplastic nevus (**c**).*

However, a combined nevus in its classical definition is composed of two distinct cellular populations. In this case, there is a gradual merging between the two components. The epithelioid elements peculiar to melanocytoma become smaller and disperse (e.g., "mature") in the deeper reaches of the lesion.

The lower portion is characterized by features resembling those both of a sclerotic common blue nevus and a desmoplastic Spitz nevus. The flat base and innocent-looking appearance of the cells in the fibrotic area rule out desmoplastic melanoma (which is only rarely pigmented).

Note that the epidermal hyperplasia customary of melanocytoma is present at one border of the lesion where there is a collarette. In the center the epidermis is normal or thinned.
These features suggest rapid growth of this part of the lesion.

This nevus was sited on the lower back of a 20-year-old male.
A Ki-67 immunostain indicated a very low level of cellular proliferation