CONJUNCTIVAL MELANOMAS: PROGNOSTIC FACTORS A REVIEW AND AN ANALYSIS OF A SERIES

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REVIEW OF THE LITERATURE

CONJUNCTIVAL MELANOMAS ARE RARE.[12,14,23] A SCARCITY OF WELL-STUDIED AND published cases of conjunctival melanomas makes it difficult to assess prognostic factors for these neoplasms. Several authorities[3,21,28] have emphasized similarities between skin and conjunctival melanomas; therefore, the extensive literature on the relatively common melanoma of the skin might yield information of value in evaluating the prognosis of melanomas of the conjunctiva.

The following factors affect the prognosis of skin melanomas: the level of invasion; the mitotic rate; the location of the tumor; the type of the melanoma; the age and sex of the patient; the duration of symptoms before treatment; the size of the lesion; the presence or absence of extension into blood vessels, lymphatics, or regional lymph nodes; the presence or absence of pigment in the tumor; ulceration of the surface; and exposure of the area to actinic radiation.[13] A "prognostic score sheet," devised by Cochran[15] to predict the outcome of skin melanomas, utilizes many of these factors.

LEVEL OF INVASION

Several investigators have confirmed the relationship between the level of tumor invasion by melanomas and the mortality due to these tumors.[6,19] The level of tumor invasion referred to the following zones: epidermal, papillary dermis, reticular dermis, and subcutaneous tissue. The thickness of the tumor, measured histologically with an ocular micrometer is another method for measuring the degree of tumor invasion and correlates with the mortality of patients with malignant melanomas.[4] Patients with tumors less than 0.76 mm thick had no recurrences or metastases after excision of the

tumor; patients with lesions greater than 1.5 mm in thickness had frequent metastases.

TYPE OF MELANOMA

Primary cutaneous malignant melanomas occur in three distinct forms.[6,7,20] The rarest type of cutaneous melanoma is the lentigo maligna melanoma (circumscribed precancerous melanosis of Dubreuilh with malignant melanoma, Hutchinson's melanotic freckle with malignant melanoma). These occur on the exposed skin surfaces of elderly people (median age of 70). Various shades of tan, brown, and black color these lesions which wax and wane in the "radial growth phase" before invading the underlying dermis when they enter the "vertical growth phase." Atypical, pleomorphic, melanocytic cells occupy the basal layer of the epithelium; when invasion occurs into the dermis, the invading cells are often spindle-shaped. The most common form is superficial spreading melanoma (precancerous melanosis, "pagetoid" melanoma). This type of melanoma occurs in younger patients (median age of 56) and can develop anywhere on the body. They are less irregular in outline than lentigo maligna melanomas and are multicolored with haphazard shades of brown, grey, black, red, white and blue. Large, relatively uniform melanocytes without prominent nucleoli but with abundant "dusty" cytoplasm invade the surface epithelium in a pagetoid fashion during the radial growth phase of this tumor. The invading cells in the vertical growth phase are most often epithelioid melanoma cells. The nodular malignant melanoma, unlike the previous two melanomas, does not have a discernable radial growth phase; therefore there is no intraepithelial, spreading component. These lesions are dark brown or black but can be amelanotic. Lentigo maligna melanomas have the best prognosis; superficial spreading melanomas have the next best prognosis; and nodular melanomas have the worst prognosis. The prognosis correlates fairly well with the relative level of invasion of these three types of melanomas.

INFLAMMATORY RESPONSE

Elder, Ainsworth, and Clark[8] discussed the relationship between cellular infiltrates and malignant melanoma. They pointed out that the presence of a lymphocytic infiltrate is one of the cardinal diagnostic features of melanoma and that experimental evidence demonstrates that this infiltrate is an immune phenomena. Lymphocytes are prominent in the radial growth phase of superficial spreading melanoma and lentigo malignant melanoma but are improverished or absent in deeply invasive melanomas. They also mentioned that plasma cells have been correlated with poor prognosis,

possibly because their presence involves the production of blocking antibodies.

Thompson[25] studied the relationship of lymphocytic infiltration to the prognosis of primary melanomas of the skin. He divided his cases into three groups according to the lymphocytic response: a marked response characterized by lymphocytic infiltration of the whole lesion or of its whole base, forming a complete basal zone of infiltration; an intermediate response with an easily recognizable lymphocytic infiltration along part of the base of the tumor, while other areas have little or no lymphocytic reaction; and a slight response in which a major part in the tumor and its base have little or no lymphocytic reaction. Cases with a marked lymphocytic infiltration had a 14% death rate from melanoma; those with an intermediate infiltration had a 37% death rate from melanoma; and those with a slight response had a 54% death rate from melanoma. Hansen and McCarten[9] also found fewer tumor deaths in melanoma patients with basal lymphocytic infiltration than in those without.

OTHER PROGNOSTIC FACTORS

The previously mentioned "prognostic score sheet" includes other factors that seem to bear on the outcome of patients with melanomas. Males have a poorer prognosis than females; patients with symptoms for more than two years have a poorer prognosis than those with symptoms for less than two years. Melanomas in non-exposed rather than exposed skin, melanomas with one or more mitotic figures per high dry field, with vascular, lymphotic, or lymph node invasion, with surface elevation, and those larger than 2 cm in diameter have a significantly poorer prognosis than those without these features.[15]

Still, the most widely used and significant factor for determining the prognosis of skin melanomas is the depth of invasion determined by either Clark's levels or by Breslow's technique of measuring tumor thickness with an ocular micrometer.

CONJUNCTIVAL MELANOMAS

Can the criteria which are used to predict the prognosis for melanomas of the skin be applied to melanomas of the conjunctiva? Zimmerman[30] pointed out the problems of applying Cochran's "prognostic score sheet" to conjunctival lesions. In the Cochran classification, tumors of mucosal origin have a bad prognosis whereas tumors of the head and neck have a relatively good prognosis; conjunctival melanomas are of mucosal origin but located in the head and neck region. Melanomas in non-exposed areas have a poorer prognosis than melanomas in exposed areas; many of the diffuse

conjunctival melanomas, tumors which carry a relatively favorable prognosis, involve both exposed and non-exposed areas of the conjunctiva. In the Cochran score sheet, tumors in males, tumors with a large area, and tumors of long duration have a relatively poor prognosis. Many of the diffuse conjunctival melanomas associated with acquired melanosis have all these factors but a relatively good prognosis.

Classifying skin melanomas by their level of invasion is one of the most important aspects of their classification and very useful in predicting prognosis; this cannot be applied to conjunctival melanomas because conjunctiva, unlike skin, does not have a papillary dermis or a reticular dermis.

The relatively few studies of conjunctival melanomas do mention several factors which might be related to their prognosis.[11,21,22,24]

INVASION OF THE TUMOR BASED ON ITS THICKNESS

Using the technique of Breslow, Silvers and his colleagues[24] studied all the primary conjunctival melanomas from the Algernon B. Reese Laboratory of Ophthalmic Pathology, 17 cases of atypical melanocytic hyperplasia (*in situ* melanoma) and 28 cases of invasive melanoma. They found a striking correlation between tumor thickness and the eventual outcome of the disease. A tumor thickness of 1.5 to 2.0 mm appeared to be a critical transition between controllable and metastasizing disease. Only one patient with a tumor greater than 1.5 mm in depth survived; his melanoma measured 1.95 mm in thickness. All except two of the patients who died of disseminated melanoma had tumors greater than 1.8 mm thick. Jay,[11] on the other hand, found no difference in prognosis between superficial and deep melanomas that arose from widespread intraepithelial melanomas but mentioned that his series was small and felt that depth of invasion might prove significant in a larger series.

TYPE OF MELANOMA (LENTIGO MALIGNANT MELANOMA, SUPERFICIAL SPREADING MELANOMA, NODULAR MELANOMA)

As previously mentioned, melanomas of the skin comprise three main types: lentigo malignant melanoma, the rarest; superficial spreading melanoma, the most frequent; and nodular melanoma, which unlike the previous two does not have a radial growth phase preceeding the vertical growth phase. Melanomas in the conjunctiva with a prolonged radial growth phase have been traditionally classified as precancerous and cancerous melanosis.[21,22,28,29] Recently, Bernardino[2,3] and his colleagues, tried to classify 23 conjunctival melanomas in a fashion similar to skin melanomas. Ten patients had superficial spreading melanomas; five of these died of metastases. Five patients had lentigo maligna melanoma; four were alive

eight or more years after the tumor was excised. A significant number of the conjunctival melanomas in their series could not be adequately classified in terms relative to skin melanomas. Several authorities[10,24,30] have pointed out the difficulties in classifying conjunctival melanomas according to the criteria applied to skin melanomas; both the clinical and histologic appearance of conjunctival melanomas with a radial growth phase are different from lentigo maligna melanoma and superficial spreading melanoma in the skin. Silvers and his colleagues were unable to identify any examples of lentigo maligna or lentigo malignant melanoma of the conjunctiva and felt that most cases of precancerous and cancerous melanosis were most closely related to superficial spreading melanoma of the skin. In the end, they chose to "avoid this controversial, and probably relatively unimportant issue." Instead, they classified all in situ melanomas as "atypical melanocytic hyperplasia" (AMH) and all cases of melanomas that had invaded the substantia propria of the conjunctiva as "melanoma." Only one of the seventeen patients with AMH died of disseminated melanoma. Twelve of the twenty-eight patients with melanoma died of the disease; in these, as previously mentioned, the prognosis seemed to be related to the depth of invasion.

THE ORIGIN OF THE MELANOMA

Most authorities agree that conjunctival melanomas can arise from pre-existing nevi, from areas of acquired melanosis, or from areas without any clinical or histologic evidence of a pre-existing lesion; however, the relative importance of these precursor lesions is controversial.[11,22,24,28-30] Since nevi can occur in association with acquired melanosis, the melanotic freckle of Hutchinson and superficial spreading melanoma, it can be difficult to determine whether the nevus is the origin of some of these melanomas or merely a coincidental lesion that has been overrun by the melanoma.[2,13,30] Jay[11] found no difference in the mortality of localized melanomas subdivided according to their origin. Yanoff and Fine[27] felt that melanomas which arose from nevi had a better prognosis (20% mortality) than those that arose from acquired melanosis (40% mortality) or de novo (40% mortality).

LOCATION

Melanomas involving the caruncle, fornix, or palpebral conjunctiva seem to have a poorer prognosis than those which arise in the bulbar conjunctiva or at the limbus, but the reported cases are too few to have statistical significance.[11,24]

OTHER FACTORS

The relative effect of different forms of therapy (local excision, exenteration, or radial therapy) has not been established.[11,24] Jay did find that complete removal of the tumor appeared to give a slightly better prognosis than incomplete excision. However, he mentioned that it is often difficult, if not impossible, to determine the completeness of excision.

Despite the fact that pigment content and degree of inflammatory response influence the prognosis of skin melanomas, Jay[11] found no statistical correlation between these factors and death rates for patients with conjunctival melanomas.

REPORT OF CASES

To determine the validity of various prognostic factors, all cases of primary conjunctival melanomas received by the eye pathology laboratory between 1955 and 1974 with a follow-up of five years or longer were evaluated. Cases were eliminated from the study for the following reasons: (1) A poor clinical history. (2) Lack of tissue on major excisions. A few cases were included for which no material was available from the original excision of a nevus or area of flat, acquired melanosis but for which adequate tissue for examination was available from later recurrences. (3) A follow-up period of less than five years from the time of the first excision. (4) Cases in which a patient died of an unrelated disease less than five years from the time of the first excision of a melanoma. (Only one case had to be eliminated for this reason, a man who aspirated food and died of asphyxiation four months after exenteration of the orbit for an invasive melanoma). (5) Cases that were not primary conjunctival melanomas, such as cases of lentigo malignant melanoma involving the skin of the eyelids with conjunctival extension or involvement.

A total of 19 cases comprise the study.

The following factors were studied in each case: (1) Clinical information including age at the onset of symptoms, age of excision of the initial lesion and of recurrences, and the location of each tumor that was excised. (2) Histologic features based on an examination of as many levels of each lesion as were available for study. The following features were documented:

a) Depth of invasion in millimeters, measured from the conjunctival surface to the deepest part of the tumor with an ocular micrometer. (Sometimes this could not be determined because of insufficient tissue, extension of the tumor to the deep margin of the specimen, or sections in which the conjunctiva was cut tangentially.)

b) Mitotic rate measured as the number of mitotic figures in 40 high dry fields (40 × objective and 10 × ocular).

c) The inflammatory response graded as follows:

0 = no inflammatory cells at the base of the tumor;
1 = a few inflammatory cells at the base of the tumor;
2 = a moderate number of inflammatory cells along part of the base of the tumor but not covering the whole base of the lesion;
3 = a moderate number of inflammatory cells along the whole base of the lesion with no skip areas;
4 = an intense inflammatory infiltrate along the whole base of the neoplasm.

Most of the inflammatory cells were lymphocytes; if there were a large number of plasma cells or eosinophils, this was recorded. Occasionally no subepithelial tissue was included with the specimen (melanoma extending to all of the deep margin of the specimen); in such cases the inflammatory reaction at the base of the lesion could not be determined.

d) Completeness of excision: if tumor obviously extended to the margins of the specimen, this was recorded. Frequently not enough slides were available to determine if the excision was complete. Therefore only definite examples of incomplete excisions were recorded; these cases are undoubtedly fewer than the true number of incomplete excisions.

e) The type of melanoma. The tumors were classified according to the Silver's classification of 1978: atypical melanocytic hyperplasia if atypical melanocytes involved all levels of the conjunctival epithelium, and melanoma if atypical melanocytes extended into the substantia propria.[24]

When the melanomas had a spreading component of acquired melanosis they were also classified by Zimmerman's method.[29] Stage IA is benign acquired melanosis with minimal junctional activity, Stage IB is benign acquired melanosis with marked junctional activity. Stage IIA is cancerous melanosis with minimal invasion ("superficial malignant melanoma," "incipient malignant melanoma"). Stage IIB is cancerous melanosis with marked invasion.

In addition, they were classified according to the McGovern classification of 1973: malignant melanoma, invasive, with adjacent intraepithelial componenet, Hutchinson's melanotic freckle type; malignant melanoma, invasive, with adjacent intraepithelial component, superficial spreading

type; malignant melanoma, invasive, with adjacent intraepithelial component, unclassifiable; and malignant melanoma, invasive, without adjacent intraepithelial component (nodular melanoma).[18]

It was not always possible to "fit" conjunctival melanomas into this McGovern classification. Three individuals (an ophthalmic pathologist, a general pathologist with a special interest in ophthalmic pathology, and a general pathologist with a special interest in dermatologic pathology, particularly melanomas) independently examined each of the cases. They were classified according to the McGovern classification only when all three of these individuals independently agreed to the classification.

The statistical validity of the data generated in the study was evaluated by the Fisher exact test.

CASE REPORTS

CASE 1

At the age of 23, this woman noted a pigmented line in the inferior cul-de-sac. After a pregnancy the following year, the line began to enlarge. Excision of the lesion from the inferior fornix when she was 28 years of age revealed an invasive melanoma, 1.35 mm thick. The defect was filled with a mucous membrane graft. Eleven months later, a recurrent lesion was 1 mm in diameter and pink in color. Excisional biopsy proved the lesion was a melanoma extending to the edge of the excised tissue. The orbit was exenterated within one month. A melanoma, measuring 3.75 mm in diameter, was located in the inferior fornix. Five years later, at the age of 34, she developed metastases in her leg and died within three months. An autopsy showed metastatic melanoma in the meninges, the lungs, the mediastinum, the pericardium, the ovaries, and on the serosal surfaces of the large and small intestine.

CASE 2

A 57-year-old man had irritation and swelling of the eyelids of his left eye for nine months before he saw an ophthalmologist. Patches of melanosis were located on the palpebral conjunctiva of the upper and lower eyelids, on the bulbar conjunctiva, and in the corneal epithelium. The orbit was exenterated. Atypical melanocytic hyperplasia was located in the bulbar and palpebral conjunctiva, but a 3 mm nodule of invasive melanoma was located in the inferior fornix. The patient died of metastases at the age of 71, 14 years after the exenteration.

CASE 3

This man developed a pigmented area in the bulbar conjunctiva on the temporal side of the right eye. The area enlarged gradually for four months before it was widely excised. The lesion proved to be an area of atypical melanocytic hyperplasia, 0.12 mm in thickness (Fig 1). Two years later, a dark, vascular lesion beneath the

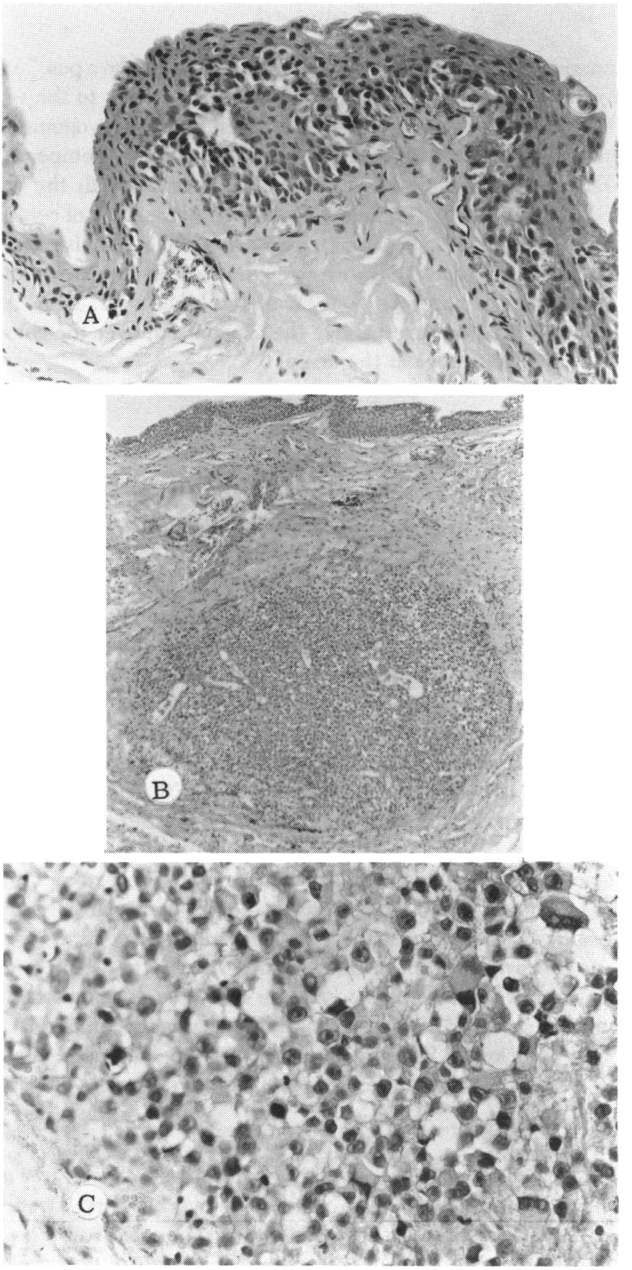


FIGURE 1

Case 3. A: Atypical melanocytic hyperplasia (×64). B: Nodule of melanoma in substantia propria beneath normal conjunctival epithelium (×17). C: Epithelioid tumor cells in the subepithelial nodule of melanoma (×100).

bulbar conjunctiva on the nasal side of the eye "shelled out like a pea." Microscopic examination showed a 5 mm nodule of melanoma extending to the edges of the specimen. Three months later, another lesion, resembling a pyogenic granuloma, developed in the area of the scar from the first excision on the temporal side of the eye. This was a 1 mm nodule of invasive melanoma beneath the conjunctival epithelium (Figs 1B and 1C). The following month, a large area of conjunctiva and soft tissue from the area of the previous excision was removed; histologic examination showed only suture granulomas with no evidence of residual neoplastic disease. Therefore, no further surgery was done. One and a half years later, a shower of subcutaneous metastases occurred above the clavicle and over the chest wall. He died of generalized metastases at the age of 33.

COMMENT

The original lesion was entirely within the epithelium. It probably spread by conjunctival lymphatics to a subepithelial location at the opposite limbus. Then it recurred in a subepithelial location at the original site.

CASE 4

A Latin-American woman had a small pigmented lesion on the bulbar conjunctiva on the temporal side of the eye for as long as she could remember. When she was 32, the lesion became irritated and increased in size (Fig 2A). The area was excised and proved to be a melanoma, invasive to depth of 0.56 mm and associated with a nevus. One year later, a new pigmented lesion appeared in the same area and another one at the limbus on the opposite (nasal) side of the eye. Both of these showed atypical melanocytic hyperplasia confined to the epithelium (Fig 2B). The following year, three pigmented lesions appeared, one on the temporal side of the eye, one inferior to the limbus nasally, and one in the inferior fornix. All three of these showed atypical melanocytic hyperplasia within the epithelium. The next month the area of pigmentation on the temporal side, which had only been partially excised, was excised. This showed atypical melanocytic hyperplasia, still confined to the epithelium. The lesion recurred within six months and extended to the superior fornix. A biopsy of this showed invasive melanoma; the orbit was exenterated two months later and showed invasive melanoma in the bulbar and palpebral conjunctiva superiorly and inferiorly. Sixteen months later, melanoma recurred in the nasopharynx; she died of metastases six years after the original biopsy.

CASE 5

When this woman was 33 years old, a mole on her right arm and an area of acquired pigmentation on the bulbar conjunctiva of the left eye were excised. The lesion on the arm was 1.7 mm thick melanoma; the lesion on the conjunctiva was reported to be a benign lentigo. Three years later another pigmented area on the conjunctiva was excised and reported to be a benign lentigo. Increasing pigmentation of the bulbar conjunctiva adjacent to the limbus nasally and superiorly occurred at the age of 42. Incisional biopsy, to confirm the clinical diagnosis of benign acquired melanosis,

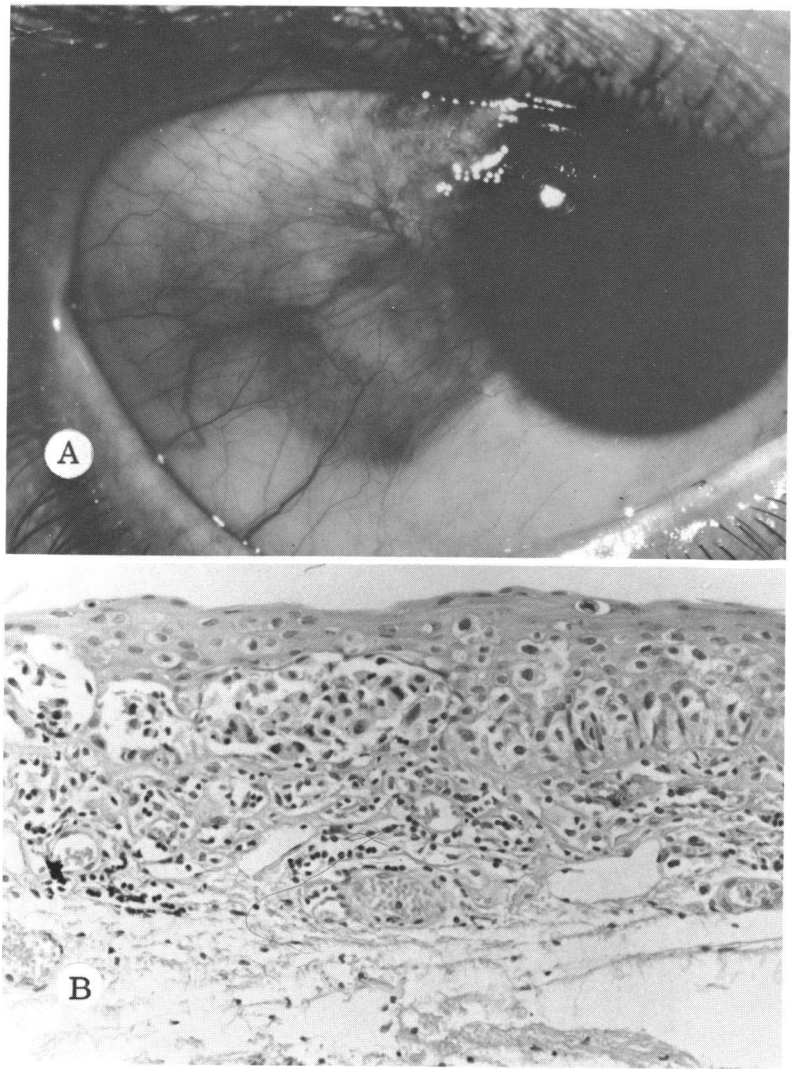


FIGURE 2
Case 4. A: Melanoma associated with a nevus. B: Atypical melanocytic hyperplasia. Note the pagetoid type invasion of the conjunctival epithelium by uniform malignant cells with dusty cytoplasm (×64).

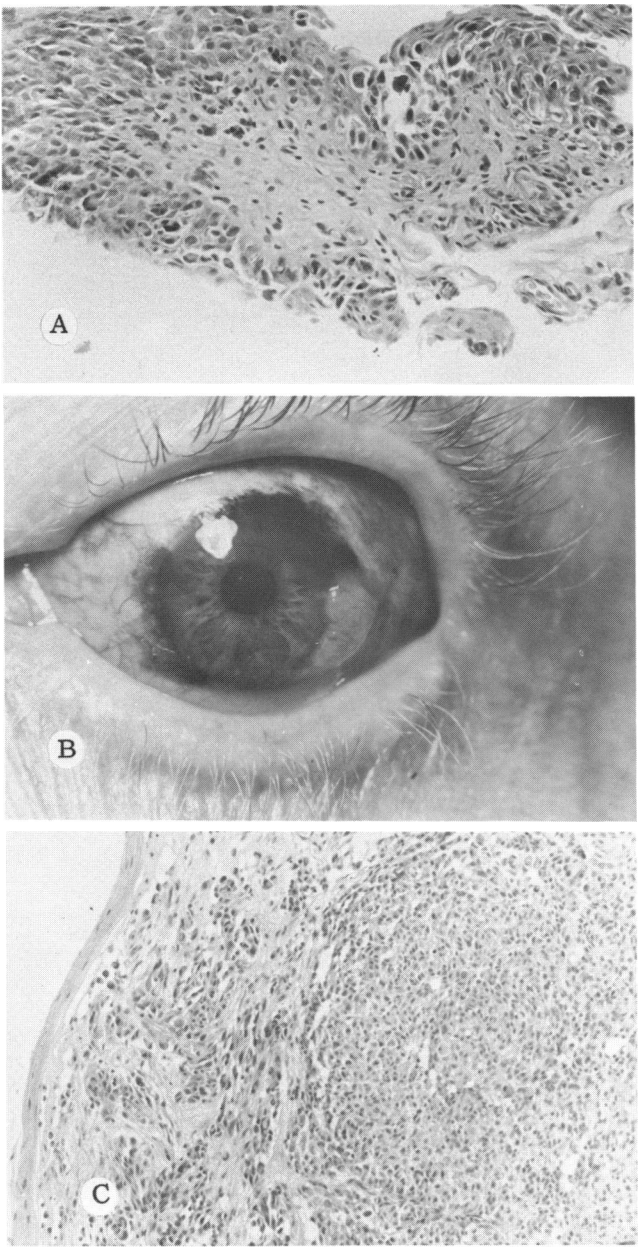


FIGURE 3

Case 5. A: Atypical melanocytic hyperplasia. Note the pleomorphic spindle shaped cells in the conjunctival epithelium (×64). B: Amelanotic nodule of melanoma at the limbus on the temporal side. Note the adjacent melanosis at the limbus superiorly and nasally. C: Amelanotic melanoma (×40).

showed atypical melanocytic hyperplasia (Fig 3A). The pigmentation nasally decreased but pigmentation superiorly and temporally increased during the next year. At the age of 43 she developed a non-pigmented nodule at the limbus on the temporal side (Fig 3B). The nodule was excised and proved to be an invasive melanoma arising adjacent to an area of atypical melanocytic hyperplasia (Fig 3C). Two months later, she died with metastases in her cerebellum, lung, gall bladder, and colon.

COMMENT

The amelanotic subepithelial melanoma which developed at the limbus of the left eye adjacent to an area of atypical melanocytic hyperplasia several months before her death from generalized metastases had the same histologic characteristics as the original arm melanoma and was most likely a metastasis. However, it could also have been a second primary melanoma arising from an area of acquired melanosis. Patients with melanoma are at high risk for developing additional primary melanomas.[26]

CASE 6

For two years, this 36-year-old Mexican-American man had noted a pigmented mass slowly, and then more rapidly, growing behind the lower lid of the right eye. The tumor was excised and proved to be an invasive melanoma, extending to the deep margin of the specimen and at least 1.9 mm in thickness. Three years later, the patient developed mediastinal metastases; he died five months later.

CASE 7

A 92-year-old Japanese man had a growing pigmented tumor at the limbus on the temporal side of the right eye, covering one-third of the cornea and protruding through the lids. He had first noticed it four months earlier. The eye was enucleated. The lesion was a melanoma, 4 mm in thickness (Figs 4A, 4B, 4C). Two years later he developed metastases in the parotid region; he died with disseminated metastases four months later.

CASE 8

This 61-year-old woman had had a pigmented lesion in the region of the caruncle of the left eye for many years but with a recent increase in size. The lesion was excised. Atypical melanocytic hyperplasia involved the epithelium and extended to the edges of the specimens (Fig 5A). During the next two years, pigmentation recurred in the area of the caruncle and extended to the superior and inferior fornix (Fig 5B). A re-excision showed atypical melanocytic hyperplasia extending to the margins of the excision, confined primarily to the epithelium, but with some areas of probable early invasion (Fig 5C). She died of metastases seven years after the initial excision.

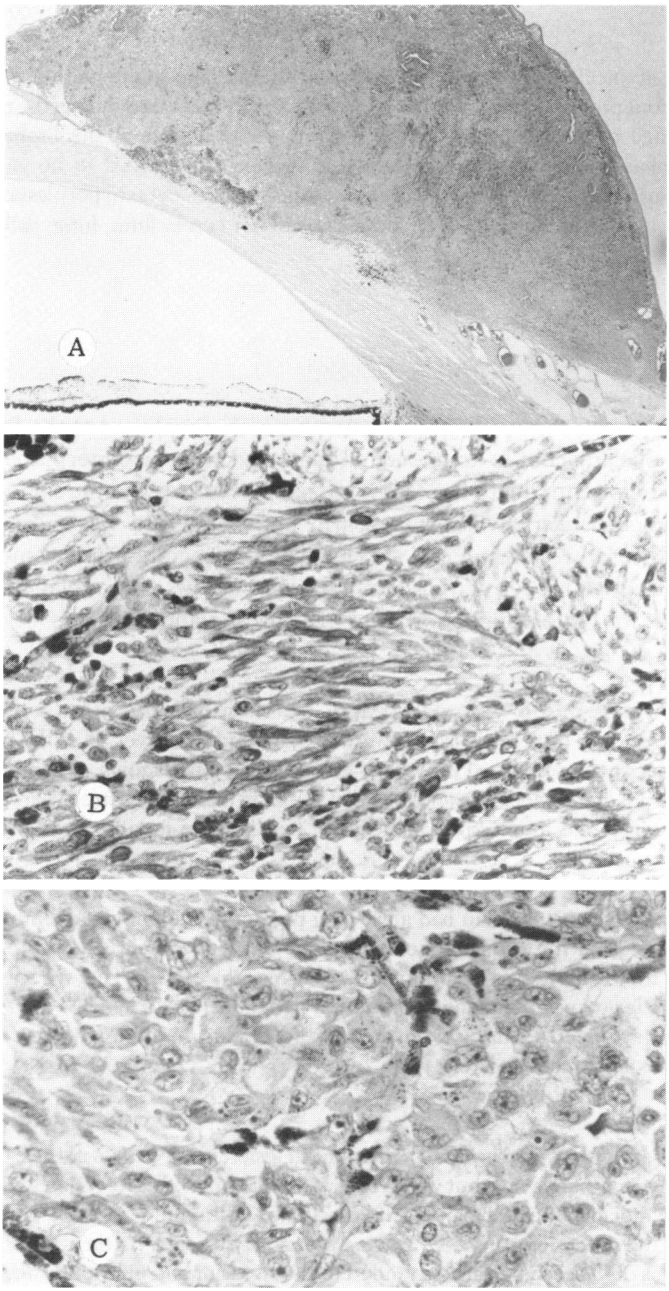
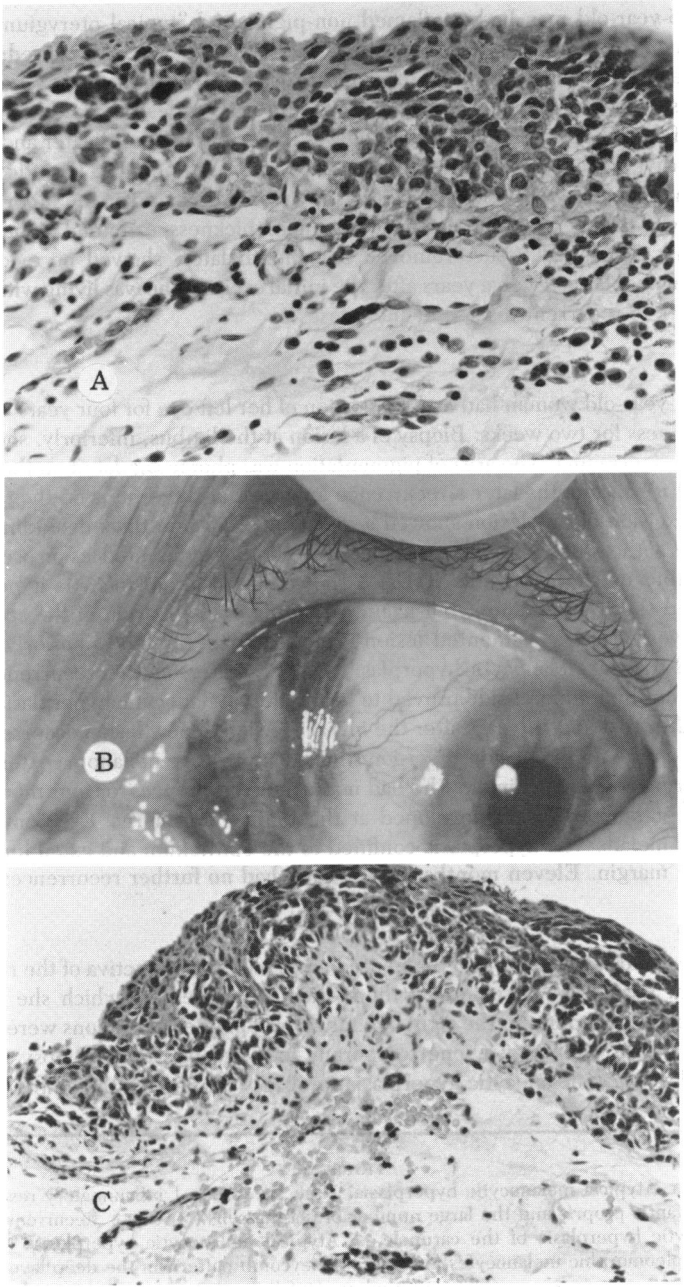


FIGURE 4

Case 7. A: Nodular melanoma at the limbus (×4). B: Spindle shaped melanoma cells in the nodular melanoma (×64). C: Epithelioid melanoma cells in the nodular melanoma (×64).


A
B
C

CASE 9

This 65-year-old man had a inflamed non-pigmented "typical pterygium" at the limbus on the nasal side of the right eye. The lesion was partially excised; the rest was treated by a McReynolds pterygium procedure. Examination of the excised tissue showed a malignant melanoma, 0.3 mm in thickness and extending to the edge of the specimen. Additional tissue was removed one month later and showed an invasive melanoma, 0.3 mm in thickness, again extending to the edges of the specimen (Figs 6A, 6B). Two years later a recurrence occurred on the superior tarsal conjunctiva. Once again a melanoma, 1.3 mm in thickness, extended to the surgical margins. Additional tissue, removed one month later, showed no evidence of residual neoplasia. Twelve years after the initial excision, he was living without any evidence of recurrent disease or metastases.

CASE 10

This 47-year-old woman had had congestion of her left eye for four years, swelling and redness for two weeks. Biopsy of a lesion at the limbus, inferiorly, showed an invasive melanoma. The area of pigmentation was photocoagulated on three occasions. Fifteen months later a recurrence appeared at the limbus on the temporal side. Excision of this lesion showed a melanoma, 0.3 mm thick extending to the margins of the specimen. Three months later, another pigmented lesion occurred at the limbus on the nasal side. Excision showed atypical melanocytic hyperplasia, confined to the epithelium, but again extending to the margin of the specimen. Three years later a pigmented lesion occurred at the limbus superiorly; biopsy showed atypical melanocytic hyperplasia. One year later, another recurrence at the limbus on the temporal side proved to be atypical melanocytic hyperplasia. Eight years after that and 14 years after the initial excision, a new lesion occurred at the limbus on the temporal side. Excision showed an invasive melanoma extending to the margins of the specimen. She had no further recurrences for four more years; then a pigmented lesion developed at the limbus superiorly. Excision showed atypical melanocytic hyperplasia confined to the epithelium and extending to the surgical margin. Eleven months later she has had no further recurrences.

CASE 11

A 61-year-old woman had had pigmented areas on the conjunctiva of the right eye for eight years. She first noticed them after an accident in which she fell and developed hematomas in the right eyelids. Three pigmented lesions were located on the bulbar conjunctiva, one temporally and two inferiorly. Biopsy of these showed atypical melanocytic hyperplasia, probably confined to the epithelium but

FIGURE 5

Case 8. A: Atypical melanocytic hyperplasia. Note the Grade 1 inflammatory response in the substantia propria and the large number of plasma cells (×100). B: Recurrent atypical melanocytic hyperplasia of the caruncle. C: Atypical melanocytic hyperplasia. Note the atypical pleomorphic melanocytes forming a honeycomb pattern in the deep layers of the epithelium (×64).

with several areas of possible early invasion. Five months later she developed a lesion in the inferior fornix. This was excised and proved to be another area of atypical melanocytic hyperplasia. She died 12 years after the initial excision without having had any additional recurrences of metastases.

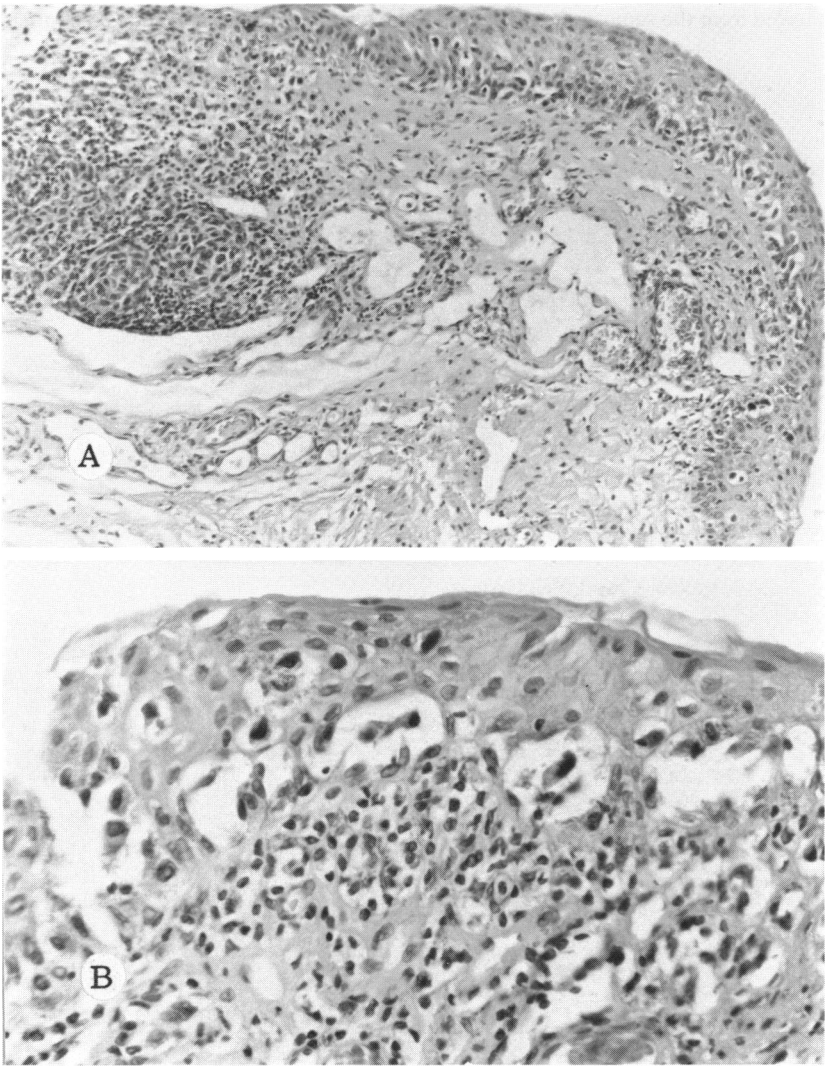


FIGURE 6

Case 9. A: Invasive melanoma on the left-hand side of the photomicrograph and pagetoid invasion of the adjacent epithelium on the right (×40). B: Pagetoid invasion of the surface epithelium adjacent to the invasive melanoma (×100).

CASE 12

A 37-year-old man had a tumor growing at the limbus of the left eye superotemporally. The lesion had been growing for nine months in an area which had been burned two years previously. Excision showed a melanoma, 0.8 mm in thickness and adjacent to a nevus (Figs 7A and 7B). Four and a half years later, a recurrence was excised from the same area and proved to be a melanoma, greater than 0.35 mm in

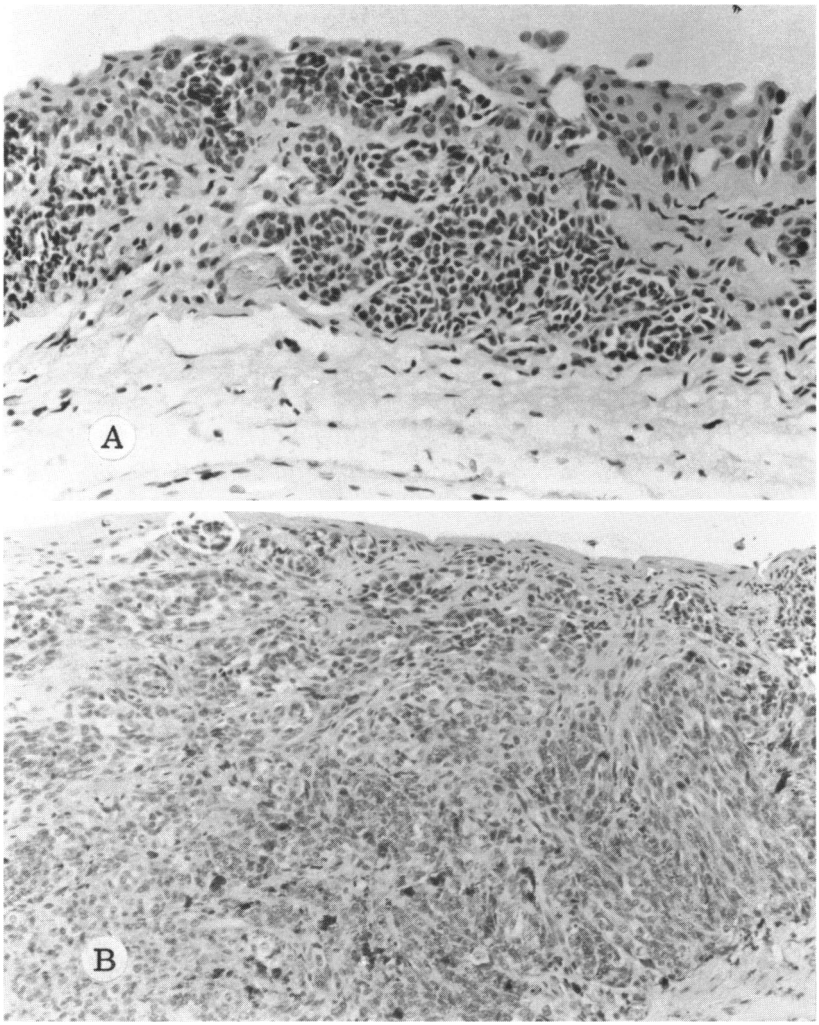


FIGURE 7

Case 12. A: Nests of benign nevus cells adjacent to the invasive melanoma in Fig 7B (×64). B: Invasive melanoma adjacent to benign nevus cells in Fig 7A (×40).

thickness and extending to the deep margin of the specimen. A second recurrence three years later (4½ years after the initial lesion was excised) was an invasive melanoma extending to the margins of the excision. Nine years after his second recurrence, he is living without any evidence of recurrence or metastases.

CASE 13

An 82-year-old man had had a pigmented lesion at the limbus on the temporal side of the right eye for over 13 years. It had been increasing in size for two years. Excision showed a melanoma, 2.2 mm in thickness and extending to the margins of the excised area (Figs 8A, 8B, 8C). Eight years later he had had no recurrences or metastatic disease.

COMMENT

Despite the thickness of this lesion, (2.2 mm) and a high mitotic index, (10 mitoses per 40 high dry fields) this patient had no recurrences or metastases for eight years.

CASE 14

A 77-year-old black woman had had a nodule at the limbus on the temporal side of the left eye for three months (Fig 9A). It appeared to be an intraepithelial carcinoma. However, examination of the excised tumor showed an invasive melanoma, 1.55 mm in thickness, adjacent to a nevus (Figs 9B, 9C, 9D). It extended to the margins of the specimen. The patient received radiotherapy but the lesion recurred in the same location five years later. The eye was enucleated. An invasive melanoma at the limbus measured 3.5 mm in thickness. She died one year later without any evidence of metastatic melanoma. At the time of enucleation, she had severe heart disease, hypertension, diabetes, and carcinoma of the large intestine. She also had a dysproteinemia.

COMMENT

Because conjunctival melanomas, like other melanomas, are rare in blacks,[11,13,27] the ophthalmologist suspected that the original pink tumor, surrounded by flat black pigment, was a carcinoma rather than a melanoma.

CASE 15

At the age of 49, this man had a pigmented lesion removed from the bulbar conjunctiva of the right eye. It was reported to be a lentigo with junctional activity. A new lesion when he was 53 was reported to be a nevus and two more lesions the same year were reported to show focal inflammation. One year later an intraepithelial melanoma was removed from the conjunctiva of the right eye. When he was 58, a pigmented lesion appeared in the palpebral conjunctiva at the superior border of

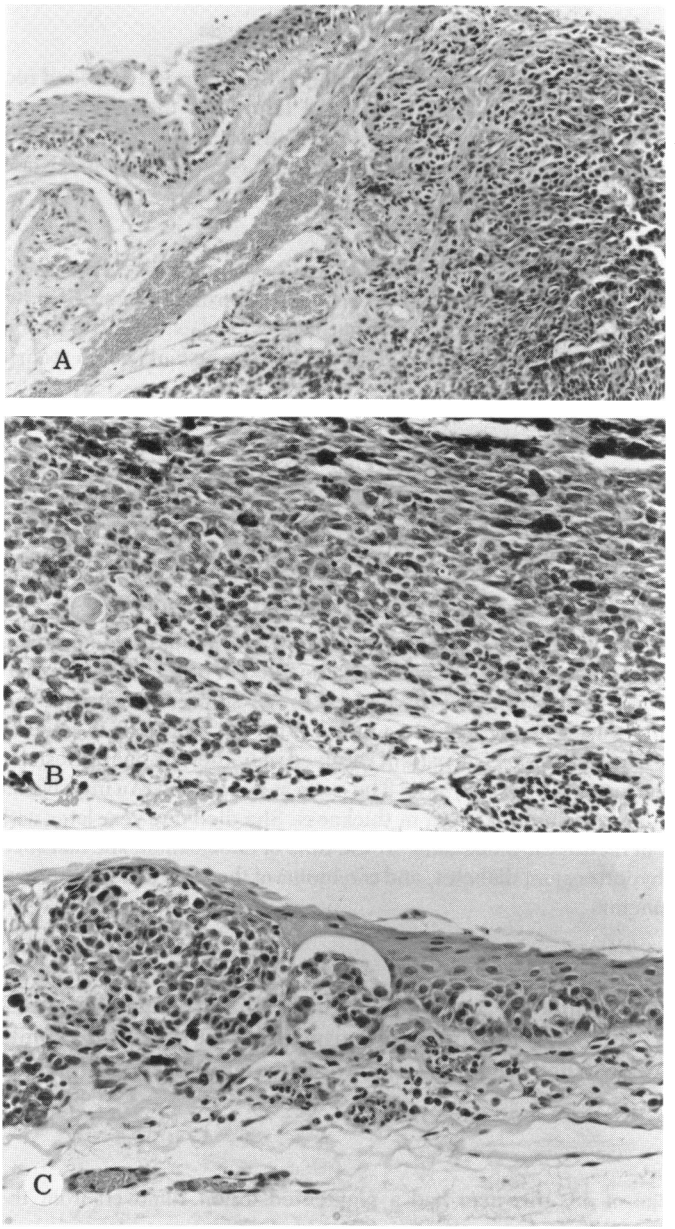
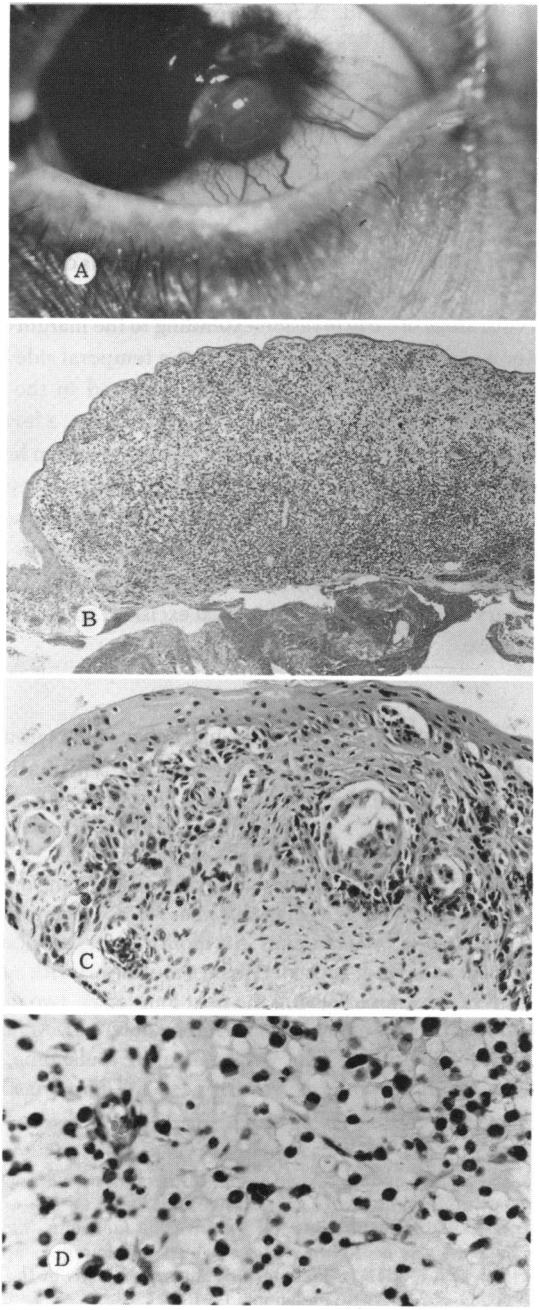


FIGURE 8

Case 13. A: Invasive melanoma on the right-hand side of the photomicrograph; atypical pleomorphic melanocytes in the basal layers of the adjacent epithelium on the left-hand side (×40). B: Spindle shaped melanoma cells at upper right; epithelioid melanoma cells at left (×64). C: Pagetoid type invasion of adjacent epithelium by relatively uniform malignant cells with dusty cytoplasm (×64).


A
B
C
D

the tarsal plate of the upper lid. A melanoma was located primarily within the surface epithelium but there were probable areas of early invasion. Four years later a small lesion at the palpebral conjunctiva inferiorly was removed; the specimen was too small to evaluate. When he was 67, pigmented lesions appeared on the tarsal conjunctiva of the right lower lid. All of these showed atypical melanocytic hyperplasia confined to the epithelium. Two years later, he has had no recurrences.

CASE 16

A tumor which had been present for two years at the limbus on the temporal side of the right eye of a 39-year-old woman was excised. The lesion was atypical melanocytic hyperplasia with areas of early invasion extending to the margin of the specimen. Three years later a recurrence at the limbus on the temporal side was excised and proved to be atypical melanocytic hyperplasia, confined to the epithelium but extending to the surgical margin (Fig 10A). Four years later, a level III superficial spreading melanoma with lymphatic invasion was removed from her abdomen (Fig 10B). Four months after this, a recurrent tumor in the right eye at the limbus inferiorly from the 3:00 to the 9:00 o'clock meridians was excised. This was an invasive melanoma extending to the margins of the specimen (Fig 10C). The abdominal melanoma recurred locally the following month and was re-excised. Six years later, 13 years after the initial conjunctival excision, she is free of recurrences or metastatic disease.

COMMENT

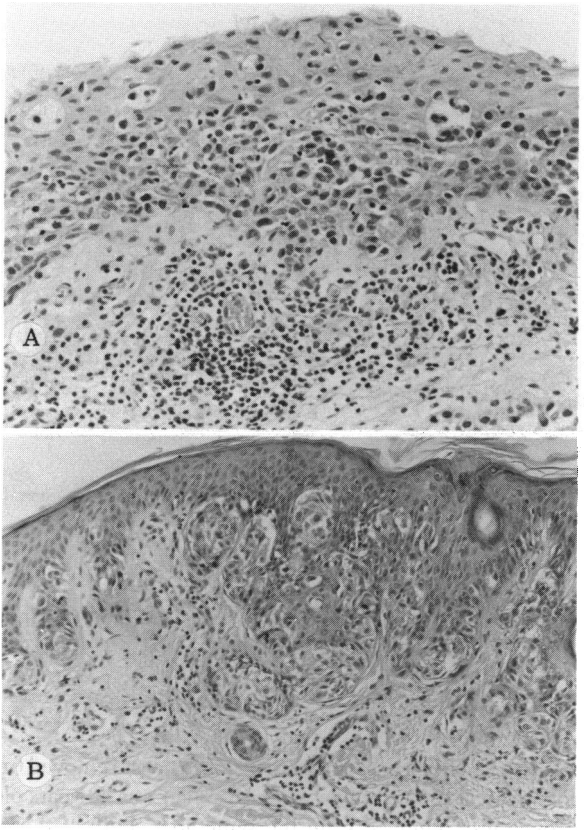
Like the patient in Case 5, this woman had a second primary melanoma. Even though it extended to level III and invaded lymphatics, she did not develop metastatic disease during the next six years.

CASE 17

A pigmented spot at the limbus on the nasal side of the right eye, present since childhood, gained pigment and size when this man was 43-years-old. The lesion was excised and reported to be a benign nevus. Six months later, a lesion recurred in the same location and was removed. It proved to be a melanoma with early invasion and measuring 0.2 mm in thickness. During the next four years, two more recurrences were removed but the reports on these could not be obtained. Another recurrence, excised 11 years after the initial lesion, was an invasive melanoma, at least 0.5 mm thick. Two years later, he has had no recurrences and no metastases.

FIGURE 9

Case 14. A: Pink amelanotic nodule of melanoma at the limbus with spreading dark pigment in the adjacent epithelium above. B: Invasive melanoma (×10). C: Junctional nevus with malignant transformation at the edge of the invasive melanoma in Fig 9B. Note the small epithelial inclusions beneath the surface which are found in approximately two-thirds of conjunctival nevi (×64). D: Pleomorphic melanoma cells in the invasive melanotic melanoma (×100).


A
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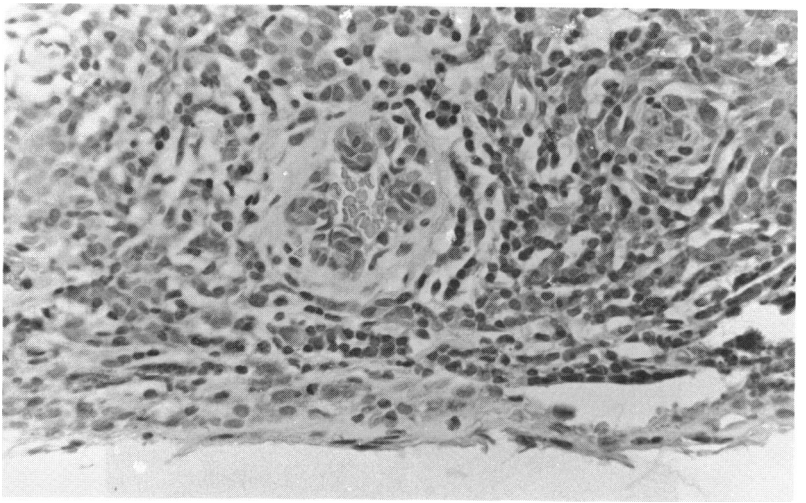

FIGURE 11
Case 19. Vascular invasion by melanoma cells (in the center of this photomicrograph) (×100).

CASE 18

A red tumor, which had been present for two months, was removed from the limbus on the temporal side of the right eye when this man was 40 years old. Four years later a recurrence was removed from the same area. Both of these lesions were reported to be active junctional nevi with early malignant change. Six months later, a recurrence at the limbus inferiorly showed cancerous melanosis. Six months after this, a recurrence at the limbus on the temporal side was excised and proved to be a melanoma with early invasion, 0.35 mm thick. Six months later, another tumor in the same area was a melanoma, 0.3 mm thick. This extended to the surgical margins of the specimen. Three months after that, another lesion appeared at the limbus on the nasal side, a lesion which proved to be a melanoma beneath the surface epithelium incorporated in scar tissue from a previous excision. Another lesion from the tarsal conjunctiva superiorly was atypical melanocytic hyperplasia confined to the epithelium. The eye received radiotherapy after this excision and has had no further recurrences during the next six years.

FIGURE 10
Case 16. A: Atypical melanocytic hyperplasia (×64). B: Superficial spreading melanoma from the abdomen. Note the similarities between the spreading intraepithelial component in this photomicrograph and the atypical melanocytic hyperplasia in the conjunctiva (Fig 10A) (×40). C: Recurrent conjunctival melanoma extending to the deep (inked) margin of the specimen at the bottom of the photomicrograph (×64).

CASE 19

At the age of 73, this woman had a pigmented lesion involving the limbus of the left eye from the 12:00 to the 3:00 o'clock meridians. The lesion was excised and proved to be an invasive melanoma, at least 0.7 mm thick. Eight years later, a pigmented tumor recurred at the limbus superonasally and another one at the limbus on the temporal side. The former was an invasive melanoma, at least 0.6 mm thick, showing evidence of perineural invasion, and the latter was a melanoma, at least 1 mm thick. The tumor extended to the surgical margins so the orbit was exenterated. Residual melanoma at the limbus superiorly was 0.6 mm thick and showed perineural invasion; a melanoma in the superior fornix was 1.2 mm in diameter, showed vascular invasion (Fig 11) and had two mitoses in 40 high dry fields. Five years after the exenteration, the patient is living without any recurrences or any evidence of metastatic disease.

COMMENT

This patient showed no recurrent disease five years after the orbit was exenterated despite the following supposedly poor prognostic factors: location in the fornix; greater than 1 mm thick; vascular and perineural invasion; and a relatively high mitotic index.

ANALYSIS OF CASES

The cases were divided into two groups. The first eight patients developed metastases and died of their disease. The last eleven patients did not develop metastases.

Two factors pertaining to the clinical aspects of the cases appear to relate to the prognosis for patients with conjunctival melanomas: the age at the time of the first excision and the location of the lesion. The sex of the patient and the duration of symptoms before treatment did not seem to influence the course of the disease in this relatively small group of patients.

Conjunctival melanoma in younger patients have a poorer prognosis. Table I shows the relationship between the age at the time of the first and subsequent excisions, the duration of symptoms when known, and the outcome of the disease. Five of the eight fatal cases had the initial melanoma excised before the age of 37, whereas all eleven of the non-fatal cases had their initial lesion treated after their 37th birthday. This is statistically significant ($p = 0.01$). However, the patient who was oldest in the series at the time of his initial treatment (Case 7, age 92) died of metastatic melanoma.

Recurrences seem to be the rule for conjunctival melanomas. All except one of the non-fatal cases had one or more recurrences and only three of the

TABLE I:A: CLINICAL INFORMATION: PATIENTS WHO DIED OF METASTASES

Case	Age, 1st Excision	Duration of Sx	Age, Subsequent Excisions	Age at Death
1	28	5 years	29, 29 (exenteration)	34
2	57 (exenteration)	1 year		71
3	28	4 months	30, 30	33
4	31	Childhood	32, 33, 33, 34, 34, (exenteration)	35
5	33	?	36, 42, 43	43
6	36	2 years		43
7	92	4 months		94
8	61	Many years	63	68

fatal cases died of metastases before developing a local recurrence (Table II).

Melanomas that arise in the caruncle, fornix, or palpebral conjunctiva have a poorer prognosis than those which arise on the bulbar conjunctiva. Table III shows the location of the initial melanoma. In five of the eight fatal cases, the original melanoma involved the caruncle, the fornix, or the palpebral conjunctiva, whereas none of the non-fatal cases started in these locations. This difference is statistically significant ($p = 0.05$). However, four of the eleven non-fatal melanomas eventually spread to the fornix or palpebral conjunctiva.

Five histologic features of conjunctival melanomas were evaluated: depth of tumor invasion, the rate of mitoses, the degree of the inflammatory response, the completeness of the excision, and the type of melanoma.

Contrary to expectations, the depth of the invasion in this small series of cases did not correlate statistically with the prognosis. Table IV lists the depth of invasion of the initial and subsequent lesions. Four of the eight fatal cases had or developed surface melanomas greater than 1.5 mm in

TABLE I:B: CLINICAL INFORMATION: PATIENTS WHO HAVE NOT YET HAD METASTASES

Case	Age, 1st Excision	Duration of Sx	Age, Subsequent Excisions	Age at Death
9	65	?	65, 67	77
10	47	4 years	49, 49, 52, 53, 60, 64	64
11	61	8 years	61	Died, 73
12	37	9 months	39, 42	51
13	82	13+ years		90
14	77	3 months	82	Died, 83
15	49	?	53, 54, 58, 62, 67	69
16	39	2 years	42, 47	52
17	43	Childhood	44, 48	56
18	40	2 months	44, 45, 45, 46, 46	52
19	73	?	81, 81 (exenteration)	85

TABLE II:A: CLINICAL INFORMATION: PATIENTS WHO DIED OF METASTASES

Case	Sex	Number of Recurrences	Age at Death	Years From 1st Excision	Years From Last Excision
1	F	1	34	6	5
2	M	0	71	14	14
3	M	2	33	5	3
4	F	3	35	4	1
5	F	3	43	10	2/12
6	M	0	43	7	7
7	M	0	94	2	2
8	F	1	68	7	5

thickness but so did two of the eleven non-fatal cases. Furthermore, two of the fatal cases began as apparent *in situ* melanoma (atypical melanocytic hyperplasia). In one (Case 3) two local metastatic nodules, 5 mm in diameter and 1 mm in diameter, developed in the substantia propria of the conjunctiva before distant metastases killed the patient. In the other (Case 8) the initial melanoma and its single recurrence were confined to the conjunctival epithelium.

The average number of mitoses in 40 high dry microscopic fields did correlate with prognosis. Table V lists the mitotic rate of the initial and subsequent lesions as well as whether or not the malignancy extended to the surgical margin of the excision. Six of the eight fatal cases had a mitotic rate of four or more mitoses per 40 high dry fields in at least one of the lesions whereas only one non-fatal case had such a high rate. This is statistically significant ($p = 0.01$).

This chart also shows no relationship existed between the rate of recurrences or metastases and whether or not tumor extended to the surgical margin of the excised tissue.

TABLE II:B: CLINICAL INFORMATION: PATIENTS WHO HAVE NOT HAD METASTASES

Case	Sex	Number of Recurrences	Age, Last Exam	Years From 1st Excision	Years From Last Excision
9	M	2	77	12	10
10	F	6	64	17	10/12
11	F	1	Died, 73	12	12
12	M	2	51	14	9
13	M	0	90	8	8
14	F	1	Died, 83	5	1
15	M	5	69	20	2
16	F	2	52	13	5
17	M	2	56	13	8
18	M	5	52	12	6
19	F	1	85	12	4

TABLE III:A: LOCATION OF MELANOMA PATIENTS WHO DIED OF MELANOMA

Case	Initial Lesion	Recurrences (same location or other location)
1	Fornix	Same
2	Palpebral and bulbar conjunctiva and fornix	No recurrence
3	Bulbar conjunctiva	Other
4	Limbus	Other
5	Limbus (diffuse)	Other
6	Fornix	No recurrence
7	Limbus	No recurrence
8	Caruncle	Other

An inverse relationship between the degree of the host's inflammatory response at the base of the tumor and the likelihood of developing distant metastases is statistically significant in this study. None of the eight fatal cases had more than a Grade 2 response in the first specimen examined whereas seven of the eleven non-fatal cases had an initial inflammatory reaction of Grade 3 or 4 on the first piece of excised tissue available for evaluation ($p = 0.05$). The presence of a significant number of plasma cells

TABLE III:B: LOCATION OF MELANOMA PATIENTS WHO HAVE NOT HAD METASTASES

Case	Initial Lesions	Recurrences (same or different location)
9	Limbus	Other
10	Limbus	Other
11	Bulbar conjunctiva, 3 tumors	Other including fornix
12	Limbus	Same
13	Limbus	No recurrence
14	Limbus	Same
15	Bulbar conjunctiva	Other including palpebral conjunctiva
16	Limbus	Other
17	Limbus	Same
18	Limbus	Other including palpebral conjunctiva
19	Limbus	Other including fornix

TABLE IV:A: DEPTH OF INVASION
PATIENTS WHO DIED OF METASTASES

Case	Thickness of 1st and subsequent tumors in mm
1	1.35 ? ?
2	3
3	0.12 in situ, 5 mm nodule, 1 mm nodule
4	0.56, 0.19 in situ and 0.3 in situ, 0.12 in situ, 0.25 in situ, 2.1, 5
5	?, ?, 0.25 in situ, 1.15
6	1.9+
7	4
8	0.23 in situ, 0.11 in situ, ? early invasion

? = thickness could not be determined.
+ = tumor extended to deep margin of the specimen.

did not seem to affect the prognosis; they were present in four of eight fatal cases and four of eleven non-fatal cases (Table VI).

Attempting to classify conjunctival melanomas by the Clark-McGovern classification as proposed by Bernardino was not a success and did not predict the outcome of the disease (Table VII). Only six of the 19 cases could be definitely placed in the Clark-McGovern classification: four superficial spreading melanomas (two fatal, two non-fatal) and two nodular melanomas (one fatal, one non-fatal). Four additional melanomas in the non-fatal group had many of the histologic characteristics of superficial

TABLE IV:B: DEPTH OF INVASION
PATIENTS WHO HAD NOT HAD METASTASES

Case	Thickness of 1st and subsequent excisions in mm
9	0.3, 0.3, 1.3
10	?, 0.3, 0.3, 0.12 in situ, 0.25 in situ, ?, 0.1 in situ
11	0.1 in situ, 0.1 in situ
12	0.8, 0.35+, 0.05+
13	2.2
14	1.55, 3.5
15	?, ?, ?, ?, ?, 0.1
16	0.4, 0.2, 0.4
17	?, 0.2, 0.5+
18	?, ?, ?, 0.35, 0.5, 0.35
19	0.7+, 0.6 and 1.0+, 0.6 and 1.2

? = thickness could not be determined.
+ = tumor extended to deep margin of specimen.

TABLE V:A: MITOTIC RATE
PATIENTS WHO DIED OF METASTASES

Case	Mitotic rate in 1st and subsequent tumors	Tumor to edges of specimen (+ = yes, 0 = no)
1	20, 0, 40	0, +, 0
2	16	0
3	0, 1, 1	0, +, +
4	0, 0, 0, 0, 5, 4	0, 0, +, 0, +, 0
5	?, ?, 0, 10	?, ?, +, +
6	4	+
7	11	0
8	0, 0	+, +

spreading melanoma but did not exactly "fit" this classification. Only one case, a non-fatal one, had a predominance of features of lentigo maligna melanoma and it did not completely "fit" this classification. Five cases had to be classified as "malignant melanoma, invasive, with adjacent intraepithelial component, unclassifiable."

Only three cases (Case 4, 12, and 14) had histologic evidence of a nevus with the melanoma. One of these had a fatal outcome. One additional patient (Case 17) had had a pigmented lesion since childhood in the area of the melanoma; furthermore, the melanoma had nevoid characteristics.

This study, like those previously reported, has too few cases to evaluate the effectiveness of exenteration compared to local excision. In general, exenteration was performed only in those cases with poor prognostic

TABLE V:B: MITOTIC RATE
PATIENTS WHO HAVE NOT HAD METASTASES

Case	Mitotic rate in 1st and subsequent tumors	Tumor to edge of specimen (+ = yes, 0 = no)
9	1, 1, 1	+, +, +
10	0, 0, 0, 0, 0, 0, 0	+, +, +, 0, 0, +, +
11	0, 0	?, ?
12	0, 0, 0	0, +, +
13	10	+
14	1, 3	+, 0
15	?, ?, ?, 1, ?, 0	?, ?, ?, ?, ?, ?
16	0, 0, 0	+, +, +
17	?, 1, 1	?, ?, ?
18	?, ?, ?, 0, 0, 0	?, ?, ?, +, +, 0
19	0, 0 and 3, 0 and 2	+, +, 0

TABLE VI:A: INFLAMMATORY REACTION PATIENTS WHO DIED OF METASTASES

Case	Inflammatory reaction in 1st and subsequent tumors
1	1, 1, 1
2	2
3	0, 1, 0
4	1, 1 and 2, 0, 1, 1, 2
5	?, ?, 1, 1
6	1 (plasma cells)
7	1 (plasma cells)
8	2 (plasma cells), 3 (plasma cells)

factors: diffuse and multicentric melanomas; deeply invasive melanomas; and melanoma involving the palpebral conjunctiva or fornix. Only four patients in this series had an exenteration and in only one was this the initial procedure. Three of the four patients died of metastases; one is living but the follow-up time from exenteration is only four years. No patients had local orbital recurrences after exenteration but one (Case 4) had a recurrence in the nasal pharnyx.

DISCUSSION

Because of the relative rarity of primary conjunctival melanomas, this series, like those previously reported, suffers from a scarcity of cases. Many questions about prognostic factors for patients with conjunctival melanomas have not yet been answered. Ash[1] reported 67 cases of conjunctival melanomas but less than half of these had an adequate follow-up. He was

TABLE VI:B: INFLAMMATORY REACTION PATIENTS WHO HAVE NOT HAD DEVELOPED METASTASES

Case	Inflammatory reaction in 1st and subsequent tumors
9	3, 3, 2
10	3, 3, 2, 4, 4 (plasma cells), ?, 3 (plasma cells)
11	4, 4
12	3, ?, ?
13	1 (plasma cells)
14	2 (plasma cells), 1
15	?, ?, ?, 4, ?, 4
16	2 (plasma cells), 3 eosinophils), 3 plasma cells, eosinophils)
17	?, 3, 3
18	?, ?, ?, 3, 1, 1
19	2, 2, 1 and 2

TABLE VII:A: TYPE OF MELANOMA
PATIENTS WHO DIED OF METASTASES

Case	Classification of: Silvers	Zimmerman	McGovern
1	Melanoma	II B	?
2	AMH and melanoma	II A and II B	?
3	AMH and melanoma	II A and II B	SSM
4	Melanoma	II B and II A	SSM
5	AMH and melanoma	I B and II B	?
6	Melanoma	II B	?
7	Melanoma	NA	Nodular melanoma
8	AMH	I B, II A	?

AMH = atypical melanocytic hyperplasia.
NA = not applicable (Zimmerman's classification is only applicable to acquired melanosis with a spreading component).
? = melanoma with unclassifiable adjacent intraepithelial component.
SSM = melanoma with superficial spreading type of adjacent intraepithelial component.
LMM = melanoma with lentigo maligna (Hutchinson's melanotic freckle) type of adjacent intraepithelial component.

not able to discuss factors related to the prognosis of these tumors. Reese[21] reported 36 cases of cancerous melanomas that were followed for five years or more, but only 32 of these cases were confirmed by biopsy. Presumably some or most of these cases were included in the careful study of Silvers and his colleagues[24] who analyzed all conjunctival lesions in the files of Algernon B. Reese Laboratory. They were able to report on only 17 cases of atypical melanocytic hyperplasia and 28 cases of melanoma. One measurement that portended a poor prognosis emerged from their study: tumors greater than 1.8 mm thick. Tumors which involved the palpebral conjunctiva, fornix, or caruncle had a poorer prognosis than those which did not, but this seemed to be related to their greater thickness before discovery and excision. Bernardino and his colleagues[3] reported only 23 cases of

TABLE VII:B: TYPE OF MELANOMA
PATIENTS WHO HAVE NOT DEVELOPED METASTASES

Case	Classification of: Silvers	Zimmerman	McGovern
9	Melanoma	II B	? SSM
10	Melanoma and AMH	II B and II A	? SSM
11	AMH	I B	?
12	Melanoma	II B	SSM
13	Melanoma	II B	? SSM
14	Melanoma	II B	? SSM
15	AMH	II A	? LMM
16	AMH and melanoma	II A, II B	SSM
17	Melanoma	NA	Nodular melanoma
18	Melanoma and AMH	II B, II A	?
19	Melanoma	NA	? nodular melanoma

primary conjunctival melanoma. The type of melanoma seemed to influence the prognosis but they were only able to classify five as lentigo maligna melanoma (with a good prognosis) and ten as superficial spreading melanoma (with a poor prognosis). Jay[11] reported the largest series of patients with conjunctival melanomas: 73 localized melanomas and 31 wide spread melanomas. He thought that even his series was too small to yield more than a few prognostic factors of statistical significance. Diffuse melanomas were more fatal than localized ones; melanomas on the caruncle or palpebral conjunctiva were more fatal than those on the bulbar conjunctiva; and melanomas that were incompletely excised were more fatal than those that were adequately removed. Our present series includes only 19 cases, too few to adequately evaluate many features which might influence the prognosis for patients with conjunctival melanomas.

Another problem of this and other series is the number of years patients were followed after their initial tumors were removed. Although a five year follow-up is adequate for some malignant tumors, melanomas have a tendency to reappear after a long period of clinical quiescence.[13,14,30] In this series five of the eight patients who died developed their metastases more than five years after their initial melanomas had been removed, and one patient had no evidence of recurrent melanoma until he died of metastases 14 years after his initial tumor.

Despite these limitations, this study does demonstrate four features of conjunctival melanomas which may influence the prognosis: the patient's age at the time of the first excision; the location of the tumor; the rate of mitoses within the tumor; and the inflammatory response to the tumor.

Young people (less than 37 years old at the time of the first excision) have a poor outlook.

Melanomas in the caruncle, the fornix, or the palpebral conjunctiva have a poor prognosis. This confirms the impression of other investigators.[11,24]

Although the rate of mitoses has not been studied as a specific factor in previous series of conjunctival melanomas, this study shows that it is a significant prognostic feature of these tumors. In histologic sections of the melanomas, the presence of four or more mitotic figures in 40 high dry microscopic fields (40 × objective, 10 × ocular) usually signified a poor prognosis.

The inflammatory response at the base of the melanoma may be an indication of the patient's immunologic response to the tumor.[5,8,16,25] The significance of this response as a prognostic factor in skin melanomas has been established.[9,25] Jay[11] is the only previous investigator of conjunctival melanomas who discussed this feature; he did not find a statistically significant correlation between the inflammatory response and the prognosis.

The present study shows that the presence of a lymphocytic infiltrate in the substantia propria of the conjunctiva along the entire base of the melanoma is a good prognostic sign.

Contrary to its significance in skin melanomas and contrary to the findings of Silvers and his colleagues,[24] the thickness of the melanoma did not correlate with its prognosis. However this present series is small and even the larger series of Jay[11] did not show such a correlation. We agree with Jay that in a larger series of cases a difference in prognosis between superficial and deep melanomas might become apparent. Silvers did emphasize the importance of using step sections to evaluate the entire tumor in order to determine its maximum thickness. We did this in most cases, but in a few cases only a single section was available for study. Furthermore, a specimen of conjunctiva tends to fold and curl more than a specimen of skin. Therefore conjunctival melanomas are sometimes sectioned tangentially, making it difficult, if not impossible, to determine their true thickness.

We were unable to effectively apply the Clark-McGovern classification to conjunctival melanomas. The majority of the tumors did show an adjacent intraepithelial spreading component (radial growth phase), but the features of this component usually did not match the features of lentigo maligna melanoma or superficial spreading melanoma in the skin. For example, Case 13 (Figs 8A, B, C) shows some features of superficial spreading melanoma (pagetoid type invasion of the epithelium by uniform malignant cells with dusty cytoplasm and invasive epithelioid type melanoma cells) and some features of lentigo maligna melanoma (spindle shaped pleomorphic melanocytes in the basal layer of the epithelium and invasive spindle shaped melanoma cells). Only six cases truly "fit" the classification. Furthermore, this classification was of no use in predicting the outcome of the disease. Therefore, at this time, we prefer the simple classification of Silvers or the classification of Zimmerman when it is applicable.

SUMMARY

Review of the literature on skin melanomas discloses that the following features of these tumors have prognostic significance: the level and depth of invasion; the mitotic rate; the type of melanoma (superficial spreading melanoma, lentigo maligna melanoma, or nodular melanoma); the location of the tumor; the age and sex of the patient; the duration of symptoms before treatment; the size of the lesion; the presence or absence of pigment; the presence or absence of extension into blood vessels, lymphatics, or regional lymph nodes; ulceration of the surface of the tumor; the

presence or absence of exposure of the area to actinic radiation; and the degree of inflammatory response to the tumor. Of these characteristics, the most widely used and significant factor for determining the prognosis of skin melanomas is the depth of invasion determined by Clark's levels and by Breslow's technique of measuring tumor thickness with an ocular micrometer.

The literature on the relatively rare conjunctival melanoma suffers from a scarcity of well studied cases but does offer several factors which may have prognostic significance: the thickness of the tumor; the type and origin of the melanoma; the location of the tumor (bulbar conjunctiva, caruncle, fornix, or palpebral conjunctiva); and the method of treatment.

We evaluated all these features reported to have prognostic significance for melanomas in a series of cases received by our eye pathology laboratory. A total of 19 cases had an adequate follow-up for statistical analysis. Contrary to previous reports, the thickness of the tumor and the type of the melanoma did not correlate with its tendency to metastasize. The study did demonstrate four features which portended an unfavorable prognosis: melanomas in patients less than 37 years of age; melanomas in the caruncle, fornix, or palpebral conjunctiva; melanomas with four or more mitotic figures in 40 high dry microscopic fields; the melanomas that do not have an inflammatory response along their entire base.

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