Uveal and Cutaneous Involvement in Paraneoplastic Melanocytic Proliferation

Bilateral diffuse uveal melanocytic proliferation (BDUMP) syndrome is a rare paraneoplastic disorder characterized by bilateral diffuse infiltration of the uvea by melanocytic tumors in the presence of an associated systemic malignant neoplasm. The uveal involvement is de novo and occurs in the absence of melanocytic metastasis. Since the description by Machemer, about 22 cases have been published. The mean age at BDUMP syndrome diagnosis is 63 years (range, 34-89 years), with a preponderance in women (13:7). In half of the cases, the ocular symptoms manifest before the diagnosis of an underlying malignancy. The most common malignancies associated with BDUMP syndrome are poorly differentiated carcinomas arising from the ovaries and uterus in women and lung carcinomas in men. In a detailed study of 4 cases, Gass et al outlined the cardinal ocular signs, which included rapidly progressive cataracts in addition to the fundus changes secondary to uveal melanocytic proliferation.

In addition, cutaneous and/or mucosal focal melanocytic proliferation has also been observed in 5 cases of documented BDUMP syndrome (Table). Mucosal involvement was widespread, with pigmentation in the oral mucosa and lips, penis, and rectum. Similarly, the acquired cutaneous pigmentation appeared to be nonspecific, with vulval involvement and head, neck, and shoulder involvement. To our knowledge, there is only 1 report in which a mucosal lesion was studied histopathologically.

In our report, we present the histopathologic findings of cutaneous involvement in a 56-year-old woman with BDUMP syndrome. Because of the similarity between the histopathologic findings in the cutaneous pigmented lesions and findings observed in mucosal and uveal lesions, we suggest that the term paraneoplastic melanocytic proliferation be used, as it is more accurate than BDUMP syndrome in describing the features of this unique paraneoplastic syndrome.

Report of a Case. A 56-year-old woman sought care in July 2002 because of progressively deteriorating vision in the left eye for 6 months. She had a history of rheumatoid arthritis but not of dysplastic nevi or cutaneous melanoma. The onset of her visual symptoms coincided with the diagnosis of large cell carcinoma of the lung. She was not known to have metastasis and was receiving chemotherapy. At examination, corrected visual acuity was 20/40 OD and 20/60 OS. Anterior segment examination results were unremarkable. At ophthalmoscopic examination of the right eye, the choroid was diffusely thickened in the macular region, with extension nasal to the optic disc. The choroid also appeared to be markedly hypermelanotic, with scattered areas of orange pigmentation corresponding to the areas of choroidal thickening (Figure 1A). Lipofuscin deposits were extensive. Findings were similar in the left eye but were more marked and also revealed shallow subretinal fluid (Figure 1B). The choroidal thickening was confirmed with B-scan ultrasonography (Figure 1C and D). Fluorescein angiographic studies showed hypofluorescence in the macular region, with reticular hypofluorescence corresponding to the distribution of the orange pigment and multifocal patchy hyperfluorescence at the level of the retinal pigment epithelium in the right eye (Figure 1E). The angiographic findings were similar but more pronounced in the left eye (Figure 1F). Indocyanine green angiography...
showed multiple focal areas of hypofluorescence in the right eye (Figure 1G) and a geographic central macular hypofluorescence with surrounding small foci of hypofluorescence in the left eye (Figure 1H).

At further questioning, the patient said she had noticed multiple recent-onset pigmented lesions on her forearms and thighs for a few months (Figure 2A). About 8 circumscribed pigmented lesions between 1 and 2 mm in greatest diameter were noted. There was no mucosal involvement. One of the cutaneous lesions was excised and evaluated histopathologically. The patient died of widespread metastasis 3 months later in another hospital, and permission to perform autopsy was not given. Histopathologic examination of the cutaneous lesion showed confluent proliferation of cytologically atypical melano-
nocytes in the basal layers of the epidermis, with focal extension into the middle of the epidermis (Figure 2B). This finding conforms with severely atypical dysplastic lentigo but falls short of lentigo maligna.

Comment. The clinical findings of bilateral diffuse choroidal thickening with hyperpigmentation and extensive orange pigment deposits in the setting of large cell carcinoma of the lung were highly suggestive of paraneoplastic BDUMP syndrome with cutaneous involvement. The clinical diagnosis was supported by ancillary study results that showed choroidal thickening at ultrasonography and the characteristic fluorescein angiographic finding of multiple hyperfluorescent patches. Histopathologic examination of the cutaneous pigmented lesions revealed a confluent proliferation of atypical melanocytes in the basal layer of the epidermis. The unlikely possibilities of primary bilateral choroidal melanoma and melanocytic choroidal metastasis were also considered and excluded.

Paraneoplastic cutaneous syndromes vary in clinical appearance. Xanthomas, acanthosis nigricans, dermatomyositis, and carcinoid syndrome are some well-recognized cutaneous paraneoplastic syndromes. Paraneoplastic hyperpigmentation is known to occur with lung carcinoma and may be due to ectopic adrenocorticotropic hormone or melanocyte-stimulating hormone. Paraneoplastic acanthosis nigricans is characterized by rapid-onset velvety hyperpigmented thickening of the skin because of hyperkeratosis without proliferation of melanocytes. Rare cases of lentigo maligna-like lesions have been reported in association with chemotherapy, but in this case the skin lesions manifested prior to chemotherapy. To our knowledge, paraneoplastic focal cutaneous and mucosal melanocytic proliferation has been observed only in the setting of BDUMP syndrome. Clinically, such lesions appear as new-onset nevi in the skin and acquired spotty pigmentation in the mucous membranes. Histopathologically, findings in the 1 previously published case involving hyperpigmentation of the lower lip showed melanocytic hyperplasia diagnosed as lentigo labialis. Findings from the cutaneous biopsy in our case were similarly categorized as lentigo. The mucocutaneous findings resembled the uveal histopathologic findings in which the uvea was laden with sheets of benign-appearing melanocytes with a minimal number of mitoses. A greater degree of anaplasia bearing close resemblance to uveal melanoma has also been observed. Results of elaborate electron microscopic and immunologic studies and suspension cell cultures suggest that uveal hyperplasia is a low-grade melanoma.

The nomenclature of BDUMP syndrome refers only to uveal involvement and does not include the full spectrum of paraneoplastic melanocytic proliferation. The prevalence of cutaneous or mucosal involvement in BDUMP syndrome is probably higher than the 20% observed in published cases because of the varying diligence with which such involvement may have been sought. There are certain embryologic and morphologic properties shared by cutaneous and uveal melanocytes because all melanocytes are derived from neural crest cells. Therefore, it is not surprising that melanocytes in the uvea and cutaneous and mucous membrane sites undergo proliferation in response to a paraneoplastic stimulus. Moreover, melanocytes in other sites, such as the meninges, may proliferate in a similar manner. Our hypothesis is supported by the fact that the histopathologic finding of melanocytic proliferation in cutaneous and mucosal lesions is similar to that observed in uveal lesions. Gass suggested the term cancer-associated melanocytopathy, but this term does not emphasize the paraneoplastic proliferation of melanocytes. We sug-
gest that the term paraneoplastic melanocytic proliferation rather than BDUMP syndrome be used to describe this entity because it more accurately reflects the clinical spectrum and pathogenesis of this unique paraneoplastic syndrome.

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Limited Wegener Granulomatosis With 40 Years of Follow-up

Wegener granulomatosis (WG) classically consists of necrotizing granulomatous inflammation of the upper and/or lower respiratory tract, necrotizing granulomatous vasculitis, usually affecting small vessels, and focal segmental glomerulonephritis. A limited form occurs, however, in which there is no renal involvement. We report a case of limited WG with apparent orbital involvement and nearly 40 years of follow-up.

Report of a Case. A 14-year-old white girl had painless swelling of her right upper eyelid and diplopia 1 week after a bout of tonsillitis in 1962. The eyelid swelling originally appeared transiently 2 to 3 months prior to the initial visit and then disappeared completely. The tonsillitis was treated with antibiotics, steroids, and tonsillectomy. Examination showed visual acuity of 20/20 OU, marked ptosis of the right upper eyelid, and a firm, nontender, immobile mass below the supraorbital rim, extending posteriorly.

A general physical examination revealed normal vital signs, lungs, heart, abdomen, and integument. Urinalysis findings were normal. The mass effect and ptosis partially improved during the next 4 months with oral corticosteroids and antibiotics. Proptosis of 2 mm OD remained. Orbital pseudotumor was tentatively diagnosed, and an anterior orbitotomy through the right upper orbitotomy was performed to allow histopathologic diagnosis. A white, fibrous, nonencapsulated mass was partially resected. The diplopia improved postoperatively but the ptosis and proptosis persisted.

Histopathologic examination revealed dense fibrous tissue containing scattered lymphoid follicles and many eosinophils (Figure 1). Neither granuloma formation nor vasculitis was seen, and a diagnosis of chronic nonspecific dacryoadenitis was made. Oral steroids, nonsteroidal anti-inflammatory medications, and chemotherapeutic agents were not used postoperatively. The patient’s right upper eyelid ptosis was corrected by levator resection in 1964.

The patient exhibited dyspnea and dysphonia in 1973 and 1979. Examination by an otolaryngologist revealed subglottic stenosis on both occasions, and the patient was treated with laser fulguration. In 1979, she additionally required a tracheostomy, which was removed uneventfully a year later. Histopathologic ex-

Figure 1. Histopathologic findings from the orbitotomy in 1962 show dense fibrous tissue and numerous eosinophils without evidence of granulomas or vasculitis.