Morphological variation of Dalén-Fuchs nodules in sympathetic ophthalmia

MICHAEL REYNARD, RALPH S RIFFENBURGH, AND DON S MINCKLER

From the Department of Ophthalmology, University of Southern California, and the Estelle Doheny Eye Foundation, Los Angeles, California, USA

SUMMARY Fifty cases of sympathetic ophthalmia were examined histologically to determine the incidence and morphology of Dalén-Fuchs nodules. At least one well-defined Dalén-Fuchs nodule was identified in 18 (36%) of the eyes examined. Three types of lesions at the level of the retinal pigment epithelium were recognised. One type was found to consist of focal hyperplasia and aggregation of retinal pigment epithelial cells. A second type, classically referred to as Dalén-Fuchs nodules, consisted of epithelioid cells and lymphocytes covered by an intact dome of retinal pigment epithelium. The third type of lesion was characterised by degeneration of the overlying retinal pigment epithelium leading to disorganisation of the Dalén-Fuchs nodule and possible release of their contents into the subretinal space. Our study demonstrated that Dalén-Fuchs nodules in sympathetic ophthalmia vary in their morphological appearance as determined by light microscopy.

Isolated nodular collections of cells lying between Bruch's membrane and the retinal pigment epithelium, in association with sympathetic ophthalmia, are classically referred to as Dalén-Fuchs nodules. The morphologic appearance of the nodular lesions was originally described in 1881 by Braley as 'small globular aggregations of unpigmented cells, in or upon the pigment epithelial layer . . . by means of which small tracts of the ciliary retina may be raised in an arch-like manner.' The classic studies by Dalén in 1904 and Fuchs in 1905 showed that these hemispherical nodular lesions consisted primarily of epithelioid cells, lymphocytes, and metaphastic cells from the retinal pigment epithelium.

Although the Dalén-Fuchs nodule is a characteristic pathologic feature of sympathetic ophthalmia, found in both sympathising and exciting eyes, it is not pathognomonic for this entity. Dalén-Fuchs nodules have also been reported in sarcoidosis, tuberculosis, and the Vogt-Koyanagi-Harada syndrome.

The purpose of this study is to describe the morphological variation of Dalén-Fuchs nodules in sympathetic ophthalmia.

Materials and methods

Fifty histologically verified cases of sympathetic ophthalmia obtained from the pathology files of the Estelle Doheny Eye Foundation, Los Angeles, California, USA, and from cases referred to the Doheny Sympathetic Ophthalmia Study were evaluated by light microscopy to determine the incidence and morphological features of Dalén-Fuchs nodules. In 48 cases the exciting eye was examined histologically. In two unrelated cases the sympathising eye was examined histologically.

Results

INCIDENCE

The presence of at least one well-defined Dalén-Fuchs nodule was confirmed in 18 (36%) cases. This figure represents a conservative estimate, because serial sections were not available in all cases.

MORPHOLOGICAL VARIATION OF DALÉN-FUCHS NODULES

The Dalén-Fuchs nodule is recognised typically as a hemispherical mound primarily consisting of epithelioid cells and occasional lymphocytes beneath the
retinal pigment epithelium. Careful evaluation of our material revealed a morphological spectrum of lesions occurring along the retinal pigment epithelium.

The first type of lesion providing the earliest indication of Dalén-Fuchs nodule formation consists of focal hyperplasia and aggregation of retinal pigment epithelial cells (Fig. 1). The retinal pigment epithelial cells form small mounds or localised areas of stratification (Fig. 2).

The second type of lesion is characterised by the presence of well defined and closely packed collections of epithelioid cells underlying a dome of retinal pigment epithelium. These lesions are classically interpreted as Dalén-Fuchs nodules (Fig. 3). Metaplastic cells from the retinal pigment epithelium, lymphocytes, and giant cells may occasionally be found within this nodular structure (Fig. 4).
In the third type of lesion the retinal pigment epithelial dome of the Dalén-Fuchs nodule degenerates. The retinal pigment epithelium disappears first at the apex of the nodule and then completely. Degeneration of the retinal pigment epithelial dome may allow cells of the Dalén-Fuchs nodule to separate from each other and be released into the subretinal space (Fig. 5). All three types of lesions described may occur in the same case.

A clear relationship between duration of disease and morphological type of Dalén-Fuchs nodule could not be established; the three types of lesions described were found in eyes enucleated early and late in the course of sympathetic ophthalmia. Eyes with Dalén-Fuchs nodules that were enucleated relatively early in the course of sympathetic ophthalmia tended to have nodules limited to an area anterior to the equator (Table 1). Generalised involvement of Dalén-Fuchs nodules along the entire length of retinal pigment epithelium was found primarily in eyes enucleated late in the course of sympathetic ophthalmia.

**Discussion**

Our present study showed that Dalén-Fuchs nodules in sympathetic ophthalmia vary in their morphological appearance as determined by light microscopy. The earliest histological finding suggestive of Dalén-Fuchs nodule formation was focal disturbance of the retinal pigment epithelium with cellular hyperplasia and aggregation. The Dalén-Fuchs nodule appears to enlarge as a result of epithelioid cells and lymphocytes accumulating beneath a dome of retinal pigment epithelium. Ultrastructural studies indicate the pigment epithelial cells forming the dome of the Dalén-
Fuchs nodule elongate in a vertical direction to reach Bruch's membrane. As a result, a complex cage-like framework is formed within the nodule. Metaplastic cells from the retinal pigment epithelium, lymphocytes, and giant cells may occasionally be found within the Dalén-Fuchs nodule. Ultimately, the retinal pigment epithelial dome degenerates and disappears. Terms such as 'autolysis' and 'bursting' have been used by other investigators to describe the histological appearance of Dalén-Fuchs nodules in this form. The spectrum of morphological changes occurring at the level of the retinal pigment epithelium is consistent with Ernst Fuchs's original hypothesis that Dalén-Fuchs nodules undergo an evolutionary sequence of development. However, further evidence is necessary to confirm this hypothesis.

The source of cells that collect within the Dalén-Fuchs nodule is controversial. By means of detailed electron microscopic study Font and associates found that the vast majority of cells within Dalén-Fuchs nodules represented transformed retinal pigment epithelium. They concluded that epithelioid cells in Dalén-Fuchs nodules were derived from retinal pigment epithelial cells. However, using immunological and ultrastructural analysis Jakobiec and associates found that Dalén-Fuchs nodules were composed of a mixture of histiocytes, lymphocytes, and depigmented epithelial cells. These authors concluded that many of the cells comprising Dalén-Fuchs nodules are of bone marrow origin. Our observations suggested that the cellular composition of Dalén-Fuchs nodules may vary according to the morphological form sampled for analysis: Dalén-Fuchs nodules sampled early in their development may show a predominance of metaplastic epithelial cells whereas, mature Dalén-Fuchs nodules may show a mixture of cellular components.

Similarly, the correlation between fundus angiographic findings and Dalén-Fuchs nodules has been controversial. Lewis and colleagues presented fluorescein angiographic findings in a sympathising eye that showed early blockage of background fluorescence by multiple discrete lesions at the level of the retinal pigment epithelium; these lesions gradually stained during the later phases of the angiogram. Histopathological examination of the exciting eye showed multiple areas of choriocapillaris obliteration by inflammatory cells and overlying Dalén-Fuchs nodules. Sharp and coworkers reported a case with comparable histopathological and angiographic findings. In contrast Segawa and Matsuoka showed fine, hyperfluorescent dots in the posterior pole of a sympathising eye during the arterial phase; these dots corresponded in dimension with Dalén-Fuchs nodules in the exciting eye. Spitznas and other investigators described similar angiographic findings.

The morphological spectrum of Dalén-Fuchs nodules suggests that it may present a variable angiographic appearance. Blockage of choroidal fluorescence may occur when an intact dome of retinal pigment epithelium contains the cellular elements of the Dalén-Fuchs nodule; the collection of densely packed epithelioid cells covered by tight intercellular junctions of the retinal pigment epithelium provides an effective block of underlying choroidal fluorescence. Gradual accumulation of fluorescein into Dalén-Fuchs nodules may produce focal hyperfluorescence. However, degeneration of the retinal...
Morphological variation of Dalén-Fuchs nodules in sympathetic ophthalmia

pigment epithelium overlying the Dalén-Fuchs nodule may allow fluorescein dye to permeate a focus in the retinal pigment epithelium and gradually accumulate in the subretinal space. Variation in the angiographic appearance of Dalén-Fuchs nodules may therefore be related to its fluorescein permeability and morphologic form.

We concluded that the morphological spectrum of Dalén-Fuchs nodules may explain its variable histological and fluorescein angiographic presentation. The observations of our study provides a background for additional clinicopathological correlation of Dalén-Fuchs nodules in sympathetic ophthalmia.

We thank Milton Reynard and Nancy J Cramer for technical assistance.

References

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Br J Ophthalmol 1985 69: 197-201
doi: 10.1136/bjo.69.3.197

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