Lesion Morphology in Age-Related Macular Degeneration and Its Therapeutic Significance

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Objectives: To quantify and categorize the lesions of neovascular age-related macular degeneration on the basis of fluorescein angiographic morphology.

Methods: We retrospectively reviewed 3580 consecutive cases of neovascular age-related macular degeneration. The lesions were graded in terms of the location, size, and composition and categorized according to the lesion components.

Results: A comprehensive schema for lesion description and categorization is presented. There were 2642 subfoveal (73.8%), 658 juxtafoveal (18.4%), and 276 extrafoveal (7.7%) lesions. After disciform lesions were excluded, 1337 subfoveal (72.3%), 580 juxtafoveal (88.1%), and 242 extrafoveal lesions (87.7%) consisted of at least 50% choroidal neovascularization, most of which included a classic or an occult component but not both. Subfoveal lesions (mean size, 2.82 Macular Photocoagulation Study disc areas) were significantly larger than juxtafoveal (mean size, 0.89 Macular Photocoagulation Study disc areas) or extrafoveal lesions (mean size, 1.04 Macular Photocoagulation Study disc areas) (Kruskal-Wallis, P<.001), but overall the lesions were substantially smaller than those found in the major trials. It is estimated that photodynamic therapy or photocoagulation may be offered to one half to two thirds of all patients with nondisciform neovascular age-related macular degeneration.

Conclusion: The smaller lesion size and low proportion of mixed choroidal neovascularization lesions suggest that treatment benefit and eligibility may be greater in the clinical setting than previously thought.

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The Macular Photocoagulation Study (MPS) was a landmark trial that showed the prognostic and therapeutic importance of lesion morphology in age-related macular degeneration (AMD).1,2 The concept of classic and occult choroidal neovascularization (CNV) was introduced through this trial, and the subgroup analysis showed the importance of lesion component and size in treatment benefit. These findings were used to help design the subsequent treatment trials, the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) and Verteporfin in Photodynamic Therapy (VIP).3,4 Furthermore, the TAP and VIP trials demonstrated the importance of lesion composition, ie, when classic and occult components were present, treatment benefit was seen only when classic CNV accounted for at least 50% of the entire lesion.3,5 Subsequent subgroup analysis was performed on data pooled from both trials, which showed that lesion size, rather than lesion composition, was the most important predictor of treatment benefit.6 Minimally classic and pure occult CNV smaller than 4 MPS disc areas showed visual outcomes comparable to those predominantly classic CNV.

Because lesion morphology is the primary determinant of eligibility for these treatments, the importance of accurate diagnosis of lesion components becomes paramount. By nature of their design, data from major trials may not accurately reflect the true frequencies of different lesion types in the clinical setting. Such information would be useful, not only to estimate the applicability of treatments but also to determine how many health care resources should be allocated for treatment of AMD.

In this report, we offer a series of 3580 cases of neovascular AMD seen by 1 clinician (P.E.B.) at a tertiary medical retinal center from May 1, 1976, to September 30, 2001. The results on detailed quantification of lesion morphology will be given and their implications discussed in light of the current guidelines for treatment of neovascular AMD.

METHODS

This study retrospectively examined 3805 consecutive cases with a preliminary diagnosis of neovascular AMD that were initially examined at a tertiary medical retinal center from May 1976 to September 2001. The records were prospectively maintained with the aim to build...
a large clinical database on AMD. Two hundred twenty-five cases were excluded from the study because of inadequate photographs due to media opacity, poor mydriasis, or photophobia. The demographic and clinical features in the excluded group were comparable to those of the included cases. The remaining 3580 cases (2622 patients) underwent a detailed morphological evaluation.

**FUNDUS PHOTOGRAPHY AND FLUORESCIN ANGIOGRAPHY**

Before 1991, photography was performed on a fundus camera (Zeiss FF4; Zeiss, Oberkochen, Germany) using a 30° field; subsequently, a different fundus camera (Topcon TRC-50; Topcon Optical Company, Tokyo, Japan) was used with a 50° field. Color stereoscopic photographs of both maculae centered at the fovea and optic disc were taken in every patient using commercially available color transparency film (Kodachrome 25; Kodak Australasia Pty Ltd, Coburg, Australia).

After obtaining informed consent, standard rapid-sequence stereoscopic fluorescein angiography was performed in every case using black-and-white film (Ilford FP4; Ilford Anitec Ltd, Melbourne, Australia), starting at the first appearance of fluorescence in the choroidal or retinal circulation. Middle- and late-phase angiographs were taken 3, 5, and 10 minutes after injection of fluorescein. Fluorescein angiographs were printed on high-contrast transparent contact sheets.

**QUANTIFICATION OF LESION MORPHOLOGY**

Three trained photographic graders (a medical retinal specialist [P.E.B.] general physician, and specialist nurse) analyzed the photographs under masked conditions, adhering to a predefined protocol adapted from published guidelines on AMD lesion quantification. The diagnosis of lesion components was confirmed by the senior grader (the retinal specialist) in every review process. Reproducibility of lesion quantification was examined by an observer error trial, the results of which will be published in a separate report.

The color transparencies and fluorescein angiograph contact sheets were viewed using commercially available 8-diopter stereoscopic viewers (Sokkia Co Ltd, Tokyo). Five types of lesion components were defined. Classic CNV was defined as a well-demarcated lesion with bright hyperfluorescence in the early phase that shows leakage through the middle and late phases and that obscures the boundaries of this area. The persistence of hyperfluorescence and leakage distinguishes a classic CNV from a window defect. Occult CNV was defined as an irregularly elevated nonhomogeneous area of stippled hyperfluorescence in the middle phase with persistent hyperfluorescence in the late phase (type 1) or as late-phase leakage in which the source of the leakage cannot be determined from earlier-phase frames (type 2). Serous retinal pigment epithelial detachment (SRPED) was defined as a round or an oval lesion with a smooth border that shows early and persistent hyperfluorescence but little evidence of leakage. The hallmarks of SRPED are the smoothness of its contours and the homogeneity of the fluorescence.

Hemorrhage was identified by early and persistently blocked fluorescence, which corresponds to blood that is visible on color or red-free black-and-white photographs. Correlation with color or red-free black-and-white photographs was often necessary to differentiate fluorescence blocked due to a small amount of hemorrhage from that due to hyperpigmentation. A disciform lesion was defined by the presence of more than half of the lesion consisting of pale fibrous tissue. Lesion components were not quantified for disciform lesions.

The dimensions of lesion components were measured independently with the aid of the Wisconsin graticule. One MPS disc area was defined as 2.54 mm² at the retinal plane. Dimensions were corrected for different photographic magnifications. The published linear magnification factors are 2.5 for the Zeiss 30° camera (Zeiss, Oberkochen, Germany) and 1.84 for the Topcon 50° camera. These magnification factors were independently checked by measuring the corresponding retinal distances on films derived from both systems in a series of subjects. The persistence of hyperfluorescence in the middle phase with persistent hyperfluorescence in the late phase cannot be determined from earlier-phase frames. The hallmarks of SRPED are the smoothness of its contours and the homogeneity of the fluorescence.

Lesion categorization was based on the CNV component, taking into account the extent of the CNV component and the relative size of classic and occult CNV. Lesions with CNV occupying at least 50% of the total area were divided into the following 4 groups: predominantly classic with no occult, predominantly classic with occult, minimally classic, and occult with no classic. In the predominantly classic group, the classic component accounted for at least 50% of the entire lesion. In a minimally classic lesion, the classic component was present but accounted for less than 50% of the entire lesion, although the total area of CNV, including the classic and occult components, covered at least 50% of the total lesion area. Lesions consisting mostly of blood or SRPED in which the CNV component occupied less than 50% of the total area were divided into the following 2 groups: classic dominant and occult dominant. Lesions without a definable CNV component and consisting entirely of hemorrhage, SRPED, or a mixture of both were for the purposes of this report considered one group.

**DATA ANALYSIS**

We performed statistical analyses using a commercially available software package (Statistica, version 6.0; StatSoft, Melbourne, Australia). We examined the normality of distribution of continuous data qualitatively by means of histograms and quantitatively by means of the Kolmogorov-Smirnov test. We used analysis of variance to compare continuous data when the distribution was normal. For continuous variables with non-parametric distribution, we used the Kruskal-Wallis median test. We compared categorical data using the χ² test.

**RESULTS**

**STUDY POPULATION**

This study included 3580 cases from 2622 patients. The mean (SD) age of the patients was 76.3 (7.3) years. The case-specific mean (SD) age was similar at 76.4 (7.2) years. There were 901 male (34.4%) and 1721 female (65.6%) patients. The right eye was involved in 1829 cases (51.1%); the left eye in 1751 (48.9%). The mean visual acuity at presentation for the entire population was 6/39 (1.7 Snellen lines), and the median visual acuity was 6/36.
In 357 cases (10.0%), no classic or occult CNV component could be identified, and the lesion was composed entirely of hemorrhage, SRPED, or a combination of both. In 269 cases (7.5%), CNV accounted for less than 50% of the total lesion size. The CNV covered at least 50% of the lesion in 2162 cases (60.4%). Disciform lesions were found in 792 cases (22.1%).

Table 1 shows the CNV components categorized by location. There were 2642 subfoveal (73.8%), 658 juxtafoveal (18.4%), and 276 extrafoveal (7.7%) lesions. All 792 disciform lesions were located subfoveally; of the remaining 1850 subfoveal lesions, 1337 (72.3%) consisted of at least 50% CNV. In comparison, CNV occupied 50% or more of the lesion area in 580 (88.1%) of juxtafoveal and 242 (87.7%) of extrafoveal lesions. The lesion location could not be ascertained in 4 cases because of ill-defined lesion boundaries. In 3 of these, CNV occupied at least 50% of the lesion, whereas in 1, no CNV component could be identified.

**LESION CATEGORIZATION BY CNV COMPONENT**

At all 3 locations, 90% or more of the lesions in which CNV occupied at least 50% of the lesion area contained classic or occult CNV but not both. Mixed CNV lesions, which included predominantly classic CNV with occult and minimally classic CNV, accounted for 10.2% of the lesions in the subfoveal group, 5.0% in the juxtafoveal group, and 4.5% in the extrafoveal group. Minimally classic lesions tended to outnumber predominantly classic lesions with occult CNV at all 3 locations. Predominantly classic with no occult and occult with no classic lesions occurred at comparable rates, but occult with no classic lesions tended to be more common in subfoveal and juxtafoveal groups (651 vs 549 in the subfoveal group; 324 vs 227 in the juxtafoveal group), whereas the reverse was found at the extrafoveal location (108 vs 123).

Of the lesions with at least 50% CNV component, more than half were pure CNV lesions. No other lesion component apart from CNV was found in 732 cases (54.7%) in the subfoveal group, 404 (69.7%) in the juxtafoveal group, and 181 (74.8%) in the extrafoveal group. These cases accounted for 39.6%, 61.4%, and 65.6% of the entire subfoveal, juxtafoveal, and extrafoveal lesions, respectively, after disciform lesions were excluded. Other lesion components, when present, usually consisted of hemorrhage, which was found in 43.4% of subfoveal, 30.2% of juxtafoveal, and 24.0% of extrafoveal lesions with at least 50% CNV. Serous retinal pigment epithelial detachment was present in only 24 subfoveal (1.8%), 1 juxtafoveal (0.2%), and 3 extrafoveal (1.2%) lesions in which CNV occupied at least 50% of the area. When the CNV component occupied less than 50% of the lesion, SRPED was present in 78 (34.7%) of subfoveal, 15 (45.5%) of juxtafoveal, and 1 (9.1%) of extrafoveal lesions. In contrast, lesions in which no CNV component was identified were predominantly SRPED, with the SRPED component being identified in 219 (76.0%), 42 (93.3%), and 15 (65.2%) of such lesions at subfoveal, juxtafoveal, and extrafoveal locations, respectively.

**LESION SIZE**

The lesion size was not distributed parametrically, with a marked skew toward the greater lesion size. Table 2 gives the median and mean total lesion size for each of the 3 locations. Also given is the distribution of lesion size divided into 4 ordinal categories. Subfoveal lesions were significantly larger than juxtafoveal or extrafoveal lesions (Kruskal-Wallis, P<.001).

The Figure shows the mean and median size of subfoveal lesions categorized by lesion component. There was a clear trend for lesions in which CNV occupied at least 50% of the area to be smaller than the rest of the lesions (Kruskal-Wallis, P<.001). Within this group, mixed CNV lesions tended to be larger than lesions containing 1 type of CNV only, ie, predominantly classic with no occult or occult with no classic lesions. The lesion size also differed significantly among lesion types in the juxtafoveal and extrafoveal groups (Kruskal-Wallis, P<.001 for both tests), but the trends were less evident than in subfoveal lesions (data not shown).

The descriptive statistics for the individual lesion component size are given in Table 3. In the subfoveal area, the lesion component size had wide ranges and extremely skewed distributions, resulting in significant discrepancies between the mean and median values. Despite this, the standard deviations and quartile ranges were relatively narrow for classic CNV, occult CNV, and SRPED, indicating that most of the cases were distributed close to the median values. Occult CNV was more common than classic in subfoveal and juxtafoveal areas, but the two occurred in similar frequencies in the extrafoveal area. Occult lesions were generally larger than classic lesions. Hemorrhage usually occupied a small area, although it could reach enormous sizes. On average, SRPED was the largest of the lesion components, but occurred less commonly than the others.

**COMMENT**

Fluorescein angiographic identification of lesion type has become a critical part of managing neovascular AMD. The MPS and 2 photodynamic therapy (PDT) trials (TAP and
Table 2. Total Lesion Size Categorized by Location*

<table>
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<tr>
<th>Location</th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
<th>No. (%) of Cases</th>
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<tr>
<td></td>
<td>≤3</td>
<td>&gt;3 to 6</td>
<td>&gt;6 to 9</td>
</tr>
<tr>
<td>Subfoveal (n=1850)</td>
<td>1.72 (2.66)</td>
<td>2.82 (3.66)</td>
<td>1312 (70.9)</td>
</tr>
<tr>
<td>Juxtafoveal (n=689)</td>
<td>0.76 (0.72)</td>
<td>0.89 (0.93)</td>
<td>635 (96.5)</td>
</tr>
<tr>
<td>Extrafoveal (n=276)</td>
<td>0.57 (1.13)</td>
<td>1.04 (1.40)</td>
<td>257 (93.1)</td>
</tr>
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</table>

Abbreviations: IQR, interquartile range; MPS, Macular Photocoagulation Study.
*Percentages have been rounded and may not total 100. The median lesion size in the subfoveal group was significantly larger than that in the rest of the groups (Kruskal-Wallis median test, P<.001).

VIP) have shown that the natural history and treatment response are closely related to the lesion size and composition. These studies have also provided practical guidelines for identifying subgroups that are most likely to benefit from treatment. The fact that no treatment benefit was seen with certain lesion types makes appropriate patient selection even more pertinent.

If we applied the treatment guidelines derived from the MPS and the TAP and VIP trials in a clinical practice setting, what proportion of patients would be eligible for treatment? It has been estimated that 16% to 30% of patients with neovascular AMD could be treated with photocoagulation. Photodynamic therapy increases the number of patients eligible for treatment. Margherio and colleagues found that, of 1000 consecutive patients referred with AMD, 17.1% were eligible for PDT compared with 9.9% who were eligible for photocoagulation. In a consecutive series of 269 eyes examined within 1 month of symptom onset, Haddad and colleagues found that 60% of the eyes with subfoveal CNV were eligible for PDT.

In our series, 1127 (60.9%) of 1890 cases with active subfoveal CNV were found to meet the published eligibility criteria for PDT (Table 4). This represents 40.4% of the entire neovascular AMD population, after disciform lesions were excluded. This estimate was reached after excluding lesions consisting of less than 50% CNV, lesions larger than 9 MPS disc areas, all minimally classic lesions, and occult with no classic lesions larger than 4 MPS disc areas in which the visual acuity was better than 6/15. The minimum visual acuity limit of 6/96 was derived from the MPS rather than the PDT trials to reflect the guidelines published in 2002, which recommended treatment where further deterioration in vision was expected to affect the patient’s quality of life. If the treatment benefit found from combined subgroup analysis of the 2 PDT trials is taken into account, an additional 63 cases of minimally classic lesions 4 MPS disc areas or smaller would become eligible for PDT, bringing the total proportion of eligible cases to 64.3% of nondisciform subfoveal neovascular AMD.

For photocoagulation, 812 (29.1%) of all active CNV lesions were found to be eligible for treatment, representing 450 (24.3%) of subfoveal and 362 (38.8%) of juxtafoveal and extrafoveal lesions, after disciform lesions were excluded. These figures were estimated by excluding lesions that were not predominantly classic, cases with visual acuity less than 6/96, and subfoveal lesions larger than 3.5 MPS disc areas. The minimum visual acuity limit for MPS juxtafoveal CNV trial was 6/120, whereas that for the extrafoveal CNV trial was 6/30, and the limit of 6/96 used in our estimation represents a simplification of the visual eligibility criteria. Because our own clinical experience suggested that small minimally classic and occult CNV at juxtafoveal and extrafoveal locations can be adequately covered by photocoagulation, estimation of eligibility for photocoagulation was extended to such lesions. An additional 253 cases of juxtafoveal lesions 1 MPS disc area or smaller and 112 cases of extrafoveal lesions 4 MPS disc areas or smaller, which are minimally classic or occult with no classic CNV, could be treatable by photocoagulation. This represents 42.2% of all nondisciform CNV secondary to AMD. In total, PDT or photocoagulation could be offered to 53.6% of all patients presenting with active CNV if treatment guidelines are closely adhered to, and this could increase to 68.8% if the eligibility guidelines were relaxed to include smaller minimally classic and occult with no classic lesions at juxtafoveal and extrafoveal locations.

Major differences exist between lesions in our series and those reported in the TAP and VIP studies that have im-

Figure. Total lesion size for subfoveal lesions categorized by lesion component. The median values are shown in parentheses. The lesion size differed significantly among the lesion types (Kruskal-Wallis, P<.001). The central dots represent the mean values; boxes, 95% standard error; and limit lines, 99% standard error. CD indicates classic dominant lesions in which choroidal neovascularization (CNV) is less than 50% of the lesion; MC, minimally classic lesions; OD, occult dominant lesions in which CNV is less than 50% of the lesions; ONC, occult with no classic lesions; PCNO, predominantly classic with no occult lesions; and PCWO, predominantly classic with occult lesions.
important implications in terms of therapeutic outcome. In our series, there were 605 cases of subfoveal predominantly classic lesions, of which 549 (90.7%) had no occult component. Eighty-one cases were minimally classic lesions. Therefore, predominantly classic CNV outnum-
bered minimally classic CNV by 7.5:1 in our series. In the TAP study, there were actually fewer predominantly classic CNV than minimally classic CNV (160 vs 201 cases).3 Furthermore, the percentage of cases with no occult CNV in the predominantly classic group was only 56% in the TAP series. Thus, not only were predominantly classic lesions much more common in our series but most of them did not have any occult component.

The lesion size in our series also differed significantly from those of the TAP and VIP studies. The mean lesion size for predominantly classic lesions in the TAP series was 3.4 MPS disc areas.6 In our series, the mean lesion size for subfoveal predominantly classic with no occult CNV, which accounted for 90.7% of predominantly classic lesions, was 1.9 MPS disc areas (median, 1.1 MPS disc areas). The mean (median) lesion size for predominantly classic lesions with occult CNV was larger at 2.7 (2.3) MPS disc areas. Minimally classic and occult with no classic lesions were also significantly smaller than those found in the TAP and VIP studies, with the mean (median) lesion sizes of 2.6 (2.3) and 2.0 (1.5) MPS disc areas, respectively. In comparison, the mean lesion size for minimally classic CNV in the TAP series was 4.7 MPS disc areas, and for occult with no classic lesions in the VIP study, 4.3 MPS disc areas.6

The significance of the differences in lesion composition and size between our series and those reported in the TAP and VIP trials can be extrapolated from the result of the combined subgroup analysis.6 The analysis showed that lesion size was the most important predictor of treatment benefit, with smaller lesions being associated with better outcome regardless of lesion composition. The primary findings from the TAP studies demonstrated significant treatment benefit in predominantly classic lesions but not in minimally classic lesions.3,5 The outcome was especially favorable in classic with no occult lesions, in which the rate of 3 lines of vision loss was 30% in the treatment group compared with 71% in the placebo group after 2 years of follow-up.3 Thus, PDT could be expected to have a more favorable outcome in our series, which was characterized by a high proportion

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<th>Table 3. Lesion Component Size Categorized by Location</th>
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<td>Location</td>
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<td>Subfoveal</td>
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<td>Extrafoveal</td>
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Abbreviations: IQR, interquartile range; MPS, Macular Photocoagulation Study; SRPED, serous retinal pigment epithelial detachment.

<table>
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<th>Table 4. Number of Cases Eligible for Treatment*</th>
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<td>Eligibility for Photodynamic Therapy</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Active CNV lesion</td>
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<tr>
<td>Not subfoveal</td>
</tr>
<tr>
<td>CNV &lt;50%</td>
</tr>
<tr>
<td>&gt;9 MPS disc areas</td>
</tr>
<tr>
<td>VA &lt;6/96</td>
</tr>
<tr>
<td>Minimally classic</td>
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<tr>
<td>Occult &gt;4 disc areas with VA</td>
</tr>
<tr>
<td>Minimally classic ≤4 MPS disc areas</td>
</tr>
</tbody>
</table>

Abbreviations: CNV, choroidal neovascularization; MPS, Macular Photocoagulation Study; VA, visual acuity.

*Data represent stepwise adjustments made by successively applying the eligibility criteria.
of classic with no occult lesions and a significantly smaller lesion size than in the TAP or VIP series.

The large discrepancies in the prevalence of lesion types encountered in the clinical practice setting differ significantly from those of the trials, which have demonstrated the efficacy of PDT and laser photocoagulation in treating neovascular AMD. Treatment benefit is likely to be greater in the clinical setting, where the lesions tend to be smaller and consist of only 1 type of CNV. Treatment could be offered to more than half of the patients first examined with active neovascular CNV, and this could expand to include more than two thirds of the patients if eligibility criteria for photocoagulation were to be less strictly applied. Apart from demonstrating the treatment benefit, the MPS and the TAP and VIP trials have produced useful guidelines for assessing lesions in neovascular AMD that can be successfully adapted to a clinical practice.

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REFERENCES


