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Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain

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In a 3-year prospective study of 643 consecutive laparoscopies for infertility, pelvic pain, or infertility and pain, the pelvic area, the depth of infiltration, and the volume of endometriotic lesions were evaluated. The incidence, area, and volume of subtle lesions decreased with age, whereas for typical lesions these parameters and the depth of infiltration increased with age. Deeply infiltrating endometriosis was strongly associated with pelvic pain, women with pain having larger and deeper lesions. Because deep endometriosis has little emphasis in the revised American Fertility Society classification and after analyzing the diagnoses made in each class, considerations for a simplifying revision with inclusion of deep lesions are suggested. In conclusion, suggestive evidence is presented to support the concept that endometriosis is a progressive disorder, and it is demonstrated that deep endometriosis is strongly associated with pelvic pain. Fertil Steril 55:759, 1991

Endometriosis is an enigmatic disease because neither the etiology, nor the natural history, nor the precise mechanisms of the associated pelvic pain and/or infertility are completely understood. To explain the etiology, mechanisms such as menstrual regurgitation and implantation[1] and/or metaplasia[2] should be considered, whereas the amount of menstrual regurgitation,[3] the immunological response,[4,5] and the local steroid hormone environment[6] may be facilitating factors. The natural history is poorly documented, although endometriosis is widely believed to be a progressive disease. Subtle lesions were shown to be more frequent in younger women,[7] and during a 6-month follow-up period, a slight increase of typical pelvic lesions was found.[8] It remains unknown why ovarian endometriomas develop in some women only. Recently, deeply infiltrating pelvic endometriosis was described in young women,[9] and these lesions were shown to be morphologically very active and to be associated with pelvic pain.[10]

Several classifications for endometriosis exist. The Acosta classification[11] emphasizes the presence and volume of endometriomas. The revised American Fertility Society (AFS) classification[12] takes into account the extent of the disease and the amount and severity of adhesions. This study was undertaken to evaluate prospectively the incidence and the depth of infiltration of endometriotic lesions, i.e., subtle implants, small and large black puckered spots, and endometriomas in different age groups of women with infertility and in women with pelvic pain.

MATERIALS AND METHODS

Laparoscopies and Patients

All women undergoing a laparoscopy between February 1, 1987 and February 1, 1990 for infertility

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(n = 416), pelvic pain (n = 170), or both complaints (n = 57) are reviewed. Laparoscopies were performed under general anesthesia. For all endometriotic lesions, the laparoscopic appearance, the diameter of the lesion, and the depth of infiltration were carefully registered during surgery. An endometriotic lesion was classified as a white vesicle, a red vesicle, a polypoid lesion, a small black puckered spot, a larger white plaque with scarring and black puckered spots, or as an endometriotic cyst.

During 1988 and 1989, most of the lesions were photographed and subsequently excised for histologic examination using a CO_2 laser. Preliminary results of this ongoing study indeed showed the presence of endometriosis in over 80% of the biopsies, confirming the reliability of the macroscopic diagnosis of endometriosis for all types of lesions except for the red puckered peritoneal spots, which we found difficult to differentiate macroscopically from submesothelial microbleedings. Therefore, these lesions were not included in this study.

Excision of endometriosis was done with the maximum superpulse output of the Sharplan 1060 CO_2 laser (Laser Industries Ltd., Tel Aviv, Israel), which is equivalent to a continuous 15-watt beam. Minimal carbonization and a perfect visualization produced by the continuous smoke evacuation system[13] were found to be important for the safe excision of deep endometriosis. Excision was started by circumscribing the lesion and continued at the border between normal tissue and the implant that glows with a slight yellow appearance during vaporization. Although for most superficial lesions the border between endometriotic and normal tissue is obvious, this can be difficult for deep lesions. Because, by histology, endometriosis was systematically found down to the bottom of the excised tissue blocks,[10] we may conclude that during surgery the depth of infiltration was not overestimated. In many lesions, small brownish fluid-filled cysts were found down to the bottom of the endometriosis and were seen to explode under the laser beam, reassuring the surgeon that the edge between this lesion and the normal tissue was still deeper.

The depth of infiltration was assessed during and after excision by holding a graded probe or a Nehzat aspiration/irrigation cannula (Cabot Medical, Langhorn, PA) against the lesion (4 holes of 1.2 mm, total graded distance: 8.9 mm). The comparison of the surgically estimated depth with the microscopically measured depth was proven to be excellent in lesions up to 8 mm of depth, the deeper lesions generally being underestimated by 1 to 3 mm by histology.[10] This discrepancy can be explained by the fact that in lesions deeper than 1 cm the excision was done so carefully, with continuous fear of the surgeon, that the bottom was vaporized rather than excised in the continuous search to remain at the border between healthy tissue and endometriosis. It is noteworthy that deeply infiltrating endometriosis is sclerotic and hard, allowing accurate assessment of depth during excision; after excision, however, an important distortion of the remaining soft tissue occurs. Excision could be performed in all women. In five women, excision was considered incomplete because not all endometriotic tissue could be removed because of fear of the surgeon to damage the bowel, ureter, and/or uterine artery. In six women with massive adhesions, active endometriosis, and bowel involvement, the procedure was delayed to pretreat them for 3 months with a gonadotropin-releasing hormone agonist (Decapeptyl; Ipsen Biotech, Paris, France, 3.75 mg/mo); these women were not included in the study. In this series, bowel or ureter injuries did not occur during excision of deep endometriosis. In 1987, endometriomas were opened, rinsed, and vaporized; in 1988 and 1989, they were excised and the remaining ovary was closed with fibrin sealant (Tissucol; NV Immuno, Brussels, Belgium). Endometriosis was scored according to the revised AFS classification.[12] The day of the menstrual cycle was ascertained by endometrial biopsy dating[14] and/or basal body temperature charts.

Data Analysis

All data were collected during surgery into a Clipper-based data base (Nantucket, Inc., Culver City, CA) and analyzed with SAS (SAS Institute, Inc., Cary, NC).[15] From the raw data, i.e., type of lesion, diameter of lesion or endometrioma, number, and depth, we calculated the area (cm^2) and the volume (cm^3) of endometriosis for each type of lesion. The calculated volumes are slightly overestimated because the lesions were considered to be cylindrical (volume = surface area × depth). The polypoid lesions and the white and red vesicles were grouped as subtle lesions and the small and large black puckered spots were considered as typical lesions.

For the statistical evaluation, the following procedures were used: χ^2, Spearman's correlation, ANOVA, i.e., the ANOVA procedure for equal cell sizes and the general linear model (GLM) procedure for unequal cell sizes, and regression analysis (probit). Unless stated otherwise, means ± SD are indicated

Table 1 Diagnoses Made During Laparoscopy[a]

	Infertility (n = 416)	Pain (n = 170)	Infertility and pain (n = 57)
Normal	24	3	2
Adhesions	47.7	46.6	70.2
Hydrosalpinx	16.0	1.8	3.5
Other	2.8	6.0	15.8
Endometriosis	68.0	70.6	83.6
Only	46.7	43.0	18.7
+ adhesions	15.1	27.0	52.6
+ hydrosalpinx	0.7	—	—
+ adhesions + hydrosalpinx	5.5	0.6	12.3

[a] Values are percents.

for normally distributed populations and means (25 to 75th percentile) for skewed distributions.

RESULTS

Incidence of Endometriosis

During 643 consecutive laparoscopies performed for infertility (n = 416), pelvic pain (n = 170), or infertility and pain (n = 57), endometriosis was found in 68%, 71%, and 84%, respectively. This incidence did not change in 1987, 1988, and 1989 being 63%, 73%, and 66% in women with infertility, 82%, 61%, and 72% in women with pain, and 25% ($\frac{1}{4}$), 81%, and 92% in women with both complaints (GLM; indication: $P = 0.026$; year: not significant).

The increased use of video-CO_2-laserendoscopy and the progressive awareness of the association of deep endometriosis and pain during this study was clearly reflected in the figures. In 1987, 1988, and 1989, 101, 189, and 337 laparoscopies were performed, respectively, whereas the indication pain increased from 17% to 24% and to 30% and the indication pain and infertility increased from 4% to 8% and to 10%, respectively (ANOVA, $P = 0.01$).

Endometriosis was detected with equal frequencies throughout the menstrual cycle, being 82%, 74%, 77%, 82%, 67%, and 78% in the early, mid, and late follicular phase and the early, midluteal, and late luteal phase, respectively. Also subtle lesions (white or red vesicles or polypoid lesions) and typical lesions (small or large black puckered spots in white plaques) were detected with equal frequencies during the menstrual cycle.

Revised AFS Classification

Endometriosis was often associated with other pathologies such as adhesions, hydrosalpinges, or both (Table 1). In women with endometriosis and infertility 46%, 23%, 23%, and 9% were scored in classes I, II, III, or IV of the revised AFS classification, respectively; in women with pain, these percentages were 42%, 36%, 28%, and 3%, and in women with infertility and pain they were 19%, 33%, 33%, and 14%, demonstrating that this latter group had more severe disease ($P < 0.001$).

When the diagnoses made in the different classes of the revised AFS score are listed (Table 2), almost

Table 2 Pelvic Area, Volume, and Endometriotic Lesions and Adhesions Observed in the Revised AFS Classification Classes

	Revised AFS			
	I (n = 175)	II (n = 114)	III (n = 94)	IV (n = 32)
With endometrioma (%)	1	13	97	100
Depth > 6 mm (%)	3	34	15	22
Endometrioma + typical + adhesions (%)	—	—	—	1
Endometrioma + adhesions (%)	—	3	55	99
Endometrioma (%)	1	2	17	—
Endometrioma + typical (%)	0	8	23	—
Typical + adhesions (%)	1	18	3	—
Typical (%)	34	32	—	—
Subtle + typical (%)	32	32	—	—
Subtle (%)	32	5	—	—
Pelvic area (cm^2)	1.8 (0.3 to 2.1)	6.0 (2.6 to 8.0)	4.5 (0 to 6.5)	2.2 (0 to 3.3)
Volume (cm^3)[a]	0.56 (0.04 to 0.63)	2.47 (0.64 to 3.47)	1.46 (0 to 1.92)	1.4 (0 to 2.04)

[a] Volume is expressed as mean (25 to 75th percentile).

all women with endometriomas are found in classes III and IV: women with an endometrioma were 97% and 100% of classes III and IV but only 1% and 13% of classes I and II. Endometriomas and the presence of adhesions are strongly associated: in women with an endometrioma (n = 140), 64% had adhesions in contrast with only 10% of women without an endometrioma ($P < 0.001$). As could be anticipated, women in the revised AFS classes III and IV differ only slightly by the volume of their endometriomas being 42 cm^3 (range 0 to 507) and 106 cm^3 (range 2 to 541), respectively. They differ mainly in the presence of dense adhesions encapsulating ovaries and/or oviducts and by the presence of adhesions and/or endometriomas in both ovaries.

Women in the revised AFS classes I and II differentiate by the total area of pelvic endometriosis being 1.8 cm^2 and 6.0 cm^2, respectively. In women of classes III or IV, the total area is only 4.5 cm^2 and 2.2 cm^2. Also, the total volume of pelvic endometriosis, i.e., endometriomas not taken into account, is highest in women with revised AFS class II (Table 2).

Depth of Infiltration of Endometriosis

The depth of infiltration of endometriosis (Fig. 1) was found to be more than 6 mm in 9%, 24%, and 38% of women with infertility, pain, or both complaints, respectively ($P < 0.001$). Deeply infiltrating lesions were found predominantly in the rectovaginal septum and the uterosacrals and, to a lesser extent, in the uterovesical fold (Table 3). They presented macroscopically as isolated black puckered spots or as larger white plaques, with black puckered spots (Table 3). In some women, especially those with bowel involvement, only the retraction is visible at laparoscopy, and the deep endometriosis is mainly recognized by palpation and/or during excision. The very deeply infiltrating pelvic endometriosis is poorly reflected in the revised AFS classification because lesions deeper than 6 mm were found in 3%, 34%, 15%, and 22% of women in revised AFS classes I to IV, respectively (Table 2).

Type of Endometriosis and Age

In the group of women investigated, i.e., women with symptoms requesting a laparoscopy, endometriosis was detected with equal frequencies in all age groups (Table 4). All women with endometriosis taken together, it is found that with increasing age the incidence of subtle lesions, i.e., polypoid lesions and red vesicles, decreases significantly, whereas the

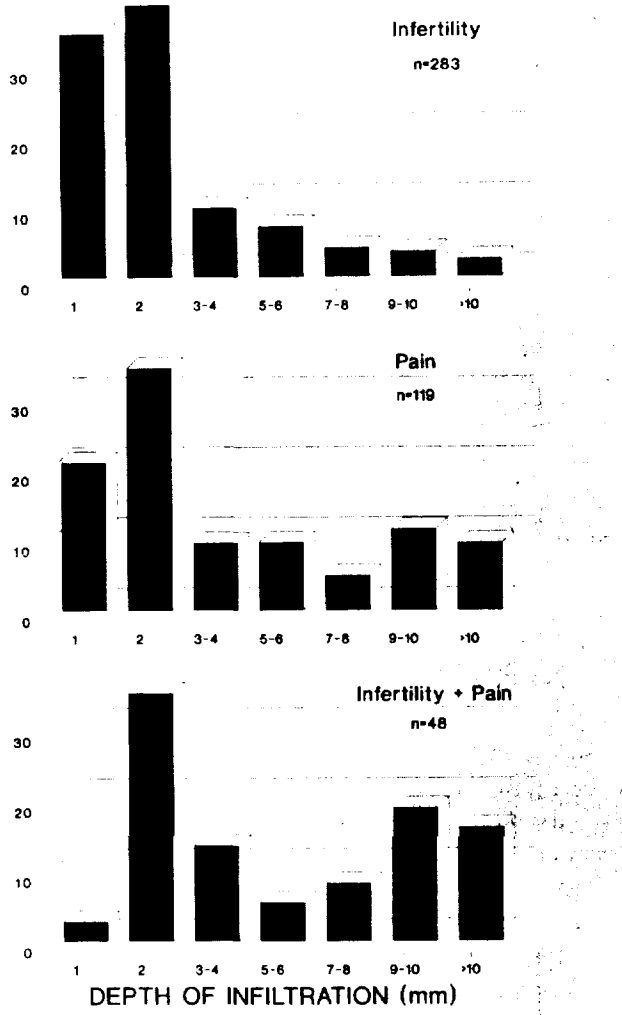

Figure 1 Frequency distributions of depth of infiltration of pelvic endometriosis in women with infertility, pain, or infertility and pain.

incidence of typical lesions, i.e., plaque type endometriosis and the incidence of endometriomas increases significantly. Also, the total volume of pelvic endometriosis (volume > 0.5 cm^3, $P = 0.05$) and the depth of infiltration (>6 mm, $P = 0.02$), but not the total pelvic area, increase significantly with age. Because women with infertility are slightly younger (29.5 years, SD is 3.9, range is 21 to 45) than women with pain (32.8 years, SD is 6.5, range is 18 to 50) or women with pain and infertility (30.6 years, SD is 4.0, range is 24 to 43), statistical significance for the effect of age was calculated after correction for the indication. Moreover, when women without an endometrioma are analyzed separately, it was found that the total area of subtle lesions ($P = 0.01$) and

Table 3 Localization and Macroscopic Aspect of Endometriosis According to the Depth of Infiltration[a]

	Depth of infiltration[b]						
	1	2	3 to 4	5 to 6	7 to 8	9 to 10	>10
Localization							
Fossa ovarica	14.5	11.3	8.5	6.5	—	—	—
Pouch of Douglas	40.3	64.6	34.3	25.8	41.2	58.6	42.1
Uterosacrals + Douglas	1.6	8.8	5.7	6.5	11.8	3.4	21.1
Uterosacrals	29.0	13.2	42.9	54.8	47.1	34.5	36.8
Uterovesical fold	14.5	11.5	8.6	6.5	—	3.4	—
Macroscopic aspect							
Allen and Masters	8	3	3	4	—	—	—
Polypoid	28	20	3	—	—	—	—
Vesicles	26	10	—	4	—	—	—
Small black puckered	14	52	54	36	35	11	30
Large black puckered	24	15	41	57	65	89	70

[a] Values are percents.

[b] Depth is measured in mm.

the total volume of subtle lesions ($P = 0.01$) decreased with age, whereas the total area of typical lesions ($P = 0.03$), the depth of infiltration ($P = 0.03$), and the volume of typical lesions ($P = 0.008$) increased with age.

Endometriosis and Pelvic Pain

Women undergoing a laparoscopy for pelvic pain or infertility and pain complained of severe chronic pelvic pain (20% and 46%), dysmenorrhea grade III (40% and 36%), deep dyspareunia (0% and 9%), or a combination of these complaints (40% and 9%) for 5.0 ± 3.7 and 2.8 ± 2.6 years, respectively. The presence of pelvic pain did not correlate with the total pelvic area of endometriosis, with subtle and typical lesions, with the total volume of subtle endometriosis, or with the volume of endometriomas but did correlate with the presence of an endometrioma ($P = 0.02$), with the total volume of endometriosis ($P = 0.01$), with the volume of typical endometriosis ($P = 0.01$), and with the depth of infiltration of the deepest lesion ($P < 0.0001$).

These findings, together with the fact that the depth of infiltration correlates with the pelvic area of endometriosis ($P < 0.001$), with the total volume of endometriosis ($P < 0.001$), and with the presence ($P < 0.001$) and the volume ($P = 0.002$) of the endometriomas, can be summarized as follows. Women with pelvic pain have larger lesions that infiltrate deeper and have more ($P < 0.001$) and larger ($P = 0.002$) endometriomas.

By multivariate analysis and logistic regression, it can be shown that once the depth of infiltration has been taken into account, neither the pelvic area,

Table 4 Age and Incidence of Endometriotic Lesions[a]

	Age					
	20 to 25 (n = 79)	26 to 30 (n = 228)	31 to 35 (n = 206)	36 to 40 (n = 92)	41 to 45 (n = 21)	Probability value[b]
With endometriosis	62	75	71	71	76	NS[c]
Subtle lesions	53.1	54.0	49.6	35.4	37.5	0.006
White vesicles	10.2	11.1	6.8	6.2	25.0	NS
Red vesicles	26.5	24.6	19.1	7.7	0.0	0.0001
Polypoid	30.6	33.9	31.3	21.5	12.5	0.03
Allen and Masters	8.2	9.9	6.8	6.2	6.2	NS
Typical lesions	57.1	56.7	61.2	64.6	75	NS
Solitary black puckered spots	46.9	40.9	44.9	38.5	25	NS
Black puckered plots in white plaques	22.5	26.3	27.9	35.4	62.5	0.0009
Endometrioma	22.5	27.5	36.7	36.9	37.5	0.018
Deep infiltration (>6 mm)	14.5	13.2	20.9	24	41.7	0.02

[a] Values are percents.

[b] Significances were corrected for the indication.

[c] NS, not significant.

nor the volume, nor the presence or the volume of endometriomas do contribute significantly to pelvic pain. The depth of infiltration thus is the most important (and the only) discriminator for pelvic pain.

DISCUSSION

The incidence of endometriosis is comparable with the highest incidences reported in the literature[16,17] and did not vary between 1987 and 1989. This is not surprising because the incidence is strongly influenced by the awareness of subtle endometriosis[17] and because of the long-standing interest of the department in these lesions.[18] Moreover, the university hospital functions as a referral center: the reported incidences thus reflect a selected group of women and are probably overestimated, in comparison with a general population. During the menstrual cycle, the incidences of endometriosis, of subtle lesions, and of typical lesions do not vary; this suggests that the laparoscopic appearance of endometriosis does not change during the menstrual cycle.

Endometriosis is generally considered as a progressive disease, but the data to substantiate this are scanty. Over a 6-month period, endometriosis increased slightly in most women,[8] but decreased in some. Serial laparoscopies over longer periods without treatment of the endometriosis would be required but are ethically and clinically difficult to perform. In a cross-sectional study, the incidence of subtle endometriosis, which is widely accepted as an early stage, was shown to decrease with age.[7] Our data confirm and extend this observation by demonstrating additionally that the incidence of typical lesions, which are considered as older and/or burnt out endometriosis, decreased with age. These observations, together with the finding that the incidence of endometriomas and that the depth of infiltration both increase with age, support the concept that endometriosis is a progressive disease. The depth of infiltration of pelvic endometriosis is comparable with the depths reported by Martin et al.[9]

Pelvic pain is known to be associated with endometriosis. In this study, a detailed analysis of the pain localization and intensity is unfortunately lacking because it was designed to evaluate the incidence, the depth of infiltration, and the volume of endometriosis. The striking differences between women undergoing a laparoscopy for pelvic pain or for infertility suggest that endometriomas, adhesions, and deep endometriosis can cause pelvic pain. Statistically, however, when the effect of deep infiltrating endometriosis is taken into account, the association of pain and endometriomas or adhesions is no longer significant. This suggests that deep infiltrating endometriosis is the main cause of pelvic pain, although the exact mechanism remains unknown. The observation of a perineural inflammatory reaction in deep endometriosis could be important.[10] The recent suggestion[19] that subtle and active lesions could cause pelvic pain is not substantiated by our data.

Deeply infiltrating endometriosis should probably be considered as a specific type of endometriosis different from superficial (and active) and intermediate (and inactive) endometriosis and from endometriomas. First, deep endometriosis is strongly associated with pelvic pain, almost all women with lesions deeper than 1 cm suffering badly. Second, the secretion of CA-125 by superficial endometriosis is directed mainly toward the peritoneal fluid, whereas deep endometriosis secretes more toward the bloodstream.[20] Third, deep endometriosis is morphologically a very active disease, whereas at intermediate depths, endometriosis is more inactive.[10] Fourth, the biphasic frequency distribution pattern (Fig. 1) suggests that deep endometriosis is another entity. We suggest that superficial endometriosis is mainly under peritoneal fluid steroid hormone control, whereas from a certain depth of infiltration (±6 mm) the hormonal environment is more influenced by plasma hormone concentrations. The specific localization of deep endometriosis in the rectovaginal septum, the uterosacrals, and the uterovesical fold is confirmed.[10]

Much effort has been devoted to develop a classification for endometriosis. Following the classification of Acosta et al.,[11] the revised AFS classification,[12] which also incorporates the presence and amount of adhesions, was developed. This is important because it reflects the difficulty of surgery, and thus the probability of conception afterward. The inherent correspondence between the two classifications is obvious from Table 2: the revised AFS classes I and II represent only 1% and 13% women with endometriomas, i.e., Acosta class I, whereas the revised AFS classes III and IV comprise almost exclusively women with endometriomas, i.e., Acosta classes II and III. The association of (larger) endometriomas and (severe) adhesions—the mechanism of which remains unclear—can explain this similarity. Indeed, endometriomas and adhesions are so strongly associated that, when increasing the points for endometriomas, adhesions could be omitted from the revised AFS classification without changing fundamentally the classification of women

Table 5 Considerations for Simplifying Changes of the Revised AFS Classification With Inclusion of the Depth of Infiltration

	Depth of deepest lesion	
	Superficial (≤6 mm)	Deep (>6 mm)
Endometrioma absent		
Pelvic area < 3 cm^2	Is	Id
Pelvic area > 3 cm^2	IIs	IId
Endometrioma present		
Endometrioma < 2 cm^3	IIIs	IIId
Endometrioma > 2 cm^3 or bilateral endometriomas or endometriomas + dense adhesions > 5 cm^2	IVs	IVd

with endometriosis. A further analysis of the revised AFS classes revealed that whereas the revised AFS classes I + II and revised AFS classes III + IV differ almost exclusively by the presence of an endometrioma, the revised AFS classes I and II differ mainly by the pelvic area and the volume involved. The revised AFS classes III and IV differ by the diameter of the endometriomas and mainly by the (bilateral) presence of extensive dense adhesions. Because of these observations, the authors believe that the AFS Classification Committee could consider a simplified revised AFS (Table 5), by which >95% of women would be classified identically but which has the advantage to be easier for use by the clinician. Because the very deep (>6 mm) endometriosis is poorly reflected in the revised AFS classification and because it probably constitutes a specific entity, the authors believe that the AFS Classification Committee should take steps to determine if these deeply infiltrating lesions influence fertility. If the effect on fertility is similar to that of its effect on pain, changes in the revised AFS classification to include deep disease could be desirable.

In conclusion, suggestive evidence is presented to substantiate that endometriosis is a progressive disease and that deeply infiltrating endometriosis is strongly associated with pelvic pain. After analyzing the incidence of lesions in each class of the revised AFS classification, considerations for simplification of the revised AFS classification and for the inclusion of deep lesions are discussed.

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