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Disseminated Peritoneal Leiomyomatosis

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Summary. Disseminated peritoneal leiomyomatosis is an unusual condition characterized by the development of numerous nodules in the peritoneal cavity which histologically have the appearance of smooth muscle tumors. The ninth proven case of this ill-understood disorder is presented here, with comments on some of the other published instances. Most reported cases were diagnosed in pregnant women, and there is good reason to believe that endocrine factors are of importance in the development of this condition. Attention is drawn to experimental studies in which an apparently similar condition has been produced in guinea pigs by endocrine manipulation. Clinically, the condition appears to be benign and the correct diagnosis is, therefore, of great importance. In the case presented here histological involution of the leiomyomatous peritoneal nodules could be demonstrated for the first time by two biopsies at an interval of 4 months – in the absence of any therapy apart from the termination of pregnancy.

Key words: Leiomyomatosis – Dissemination – Peritoneum – Pregnancy – Decidual reaction.

Introduction

In recent years a pathological picture has been described which is characterized by the development of multiple nodules of variable size, scattered all over the peritoneal cavity, and presenting the histological characteristics of leiomyomas. It has, therefore, been called "leiomyomatosis peritonealis disseminata". The condition is of great practical as well as of theoretical interest. Its practical significance lies in the fact that a mistaken diagnosis of metastatic implantation of a leiomyosarcoma could easily be made, when evidence actually

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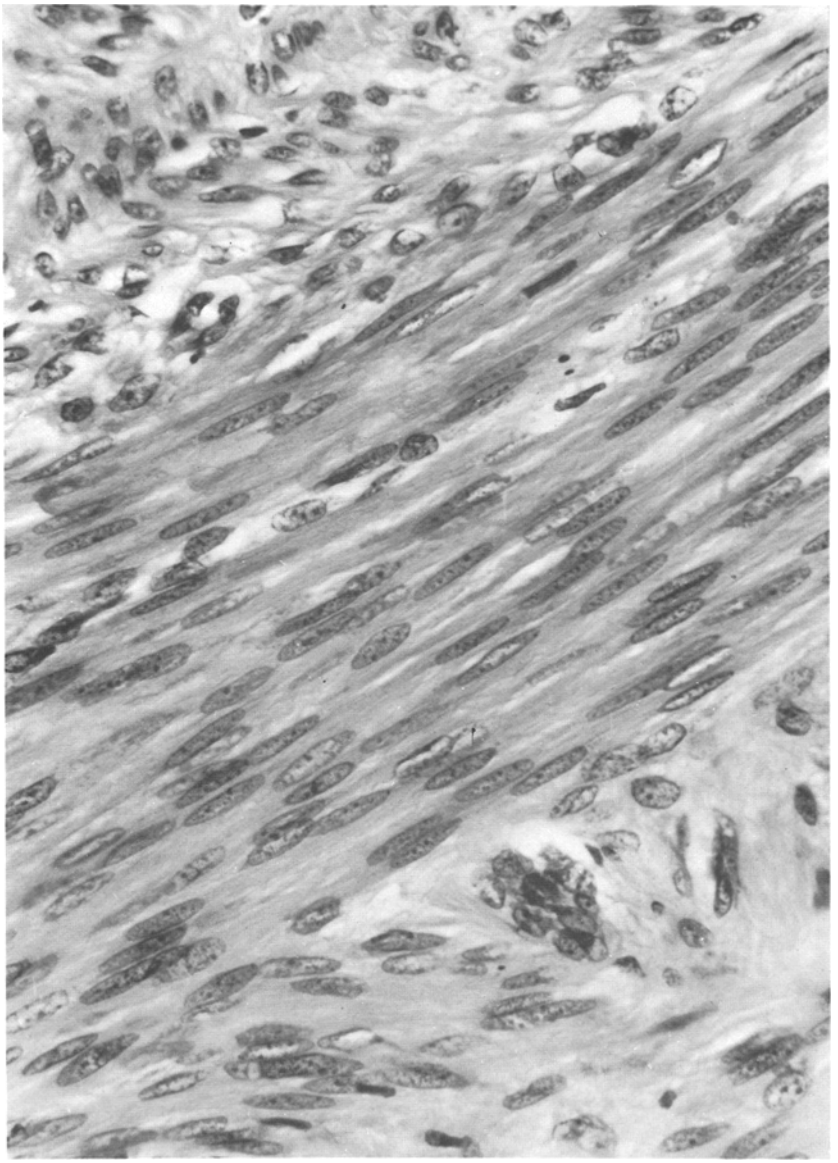

Fig. 1. Photomicrograph to show the benign histological appearance of the leiomyoma of uterus removed in October 1972. 10% buffered formalin, 6 μ, H&E, ×510

points to the condition as being benign. Its theoretical interest lies in the many questions concerning its development, which at the moment cannot be adequately answered. Since there have been only few published cases, the condition is not well known. Moreover, there has been only one previous instance in which the actual regression of the tumor nodules has been verified by a second biopsy. It was, therefore, considered of interest to report what appears to be the 9th authenticated case of disseminated peritoneal leiomyomatosis.

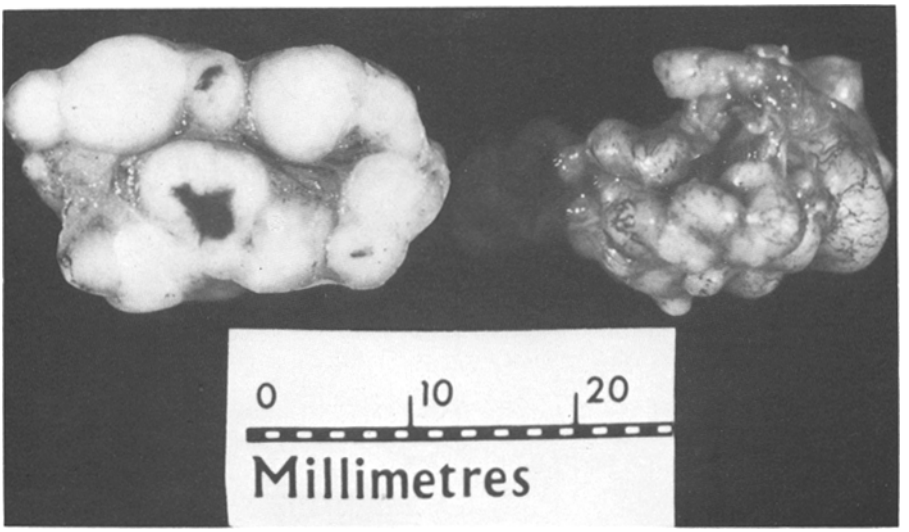

Fig. 2. Naked eye appearance of nodules (cut surface on the left) removed from omentum at time of Caesarian section in December 1975

Clinical History

A young woman of 22 years was seen in October 1972 by a general practitioner because of a complaint of swelling in the neck a year after a sub-total thyroidectomy had been performed in another hospital. A histological diagnosis of a chronic lymphocytic thyroiditis had been made at that time, and the diagnosis was subsequently confirmed also by a persistent high titre of antithyroid antibodies. The swelling of the neck at the time of examination was interpreted as being due to the enlargement of the thyroid remnant, and the patient was placed on maintenance doses of thyroid hormone. She did, however, also complain of a swelling of her abdomen. Her gynecological history stated that menarche had started at the age of 12 years. She had a menstrual cycle of 6/28–29 days. Her flow was heavy when she was taking oral contraceptives, but had been previously light. Gynecological examination showed a uterus of normal size which, however, was displaced by a swelling thought to be either a large leiomyoma or an ovarian tumor. She was advised to have a laparotomy, and a large uterine leiomyoma was removed in October 1972. Several sections did not present any significant pathological features and the tumor was considered o be benign (Fig. 1).

The patient was seen again in December 1974 at the endocrine and fertility clinic because for $1^1/_2$ years she had been unable to conceive. Examination showed a healthy young woman, 5 ft. $6^1/_2$ inches tall, weighing 140 lbs., without any obvious evidence of endocrine dysfunction. Her uterus was tender and nodular, particularly in the posterior aspects. On laparoscopy numerous adhesions in the cul-de-sac were found, so that the tubes could not be adequately visualized, but patency of the tubes could be demonstrated. The adhesions were attributed to the formation of scar tissue after the myomectomy operation two years ago. Shortly after this investigation the patient became pregnant and proceeded undisturbed to term, when a low Caesarian section had to be undertaken in December 1975 because of failure of labour to progress, and because of the onset of fetal distress. A well developed, normal female infant weighing 4300 g was delivered. In the course of the Caesarian section it was, however, noted that the peritoneum was studded with tan nodules of variable size and of rather firm consistency. The omentum was described as "firm, thick with nodularity". Numerous nodules could be seen on the broad ligaments which were "completely seeded", on the bowel, especially the sigmoid and the transverse colon, and even on the capsule of the liver. No free fluid was seen. Biopsy specimens (Fig. 2) were taken in the area of the peritoneal reflexion, the omentum, and from one of the nodules on the bowel.

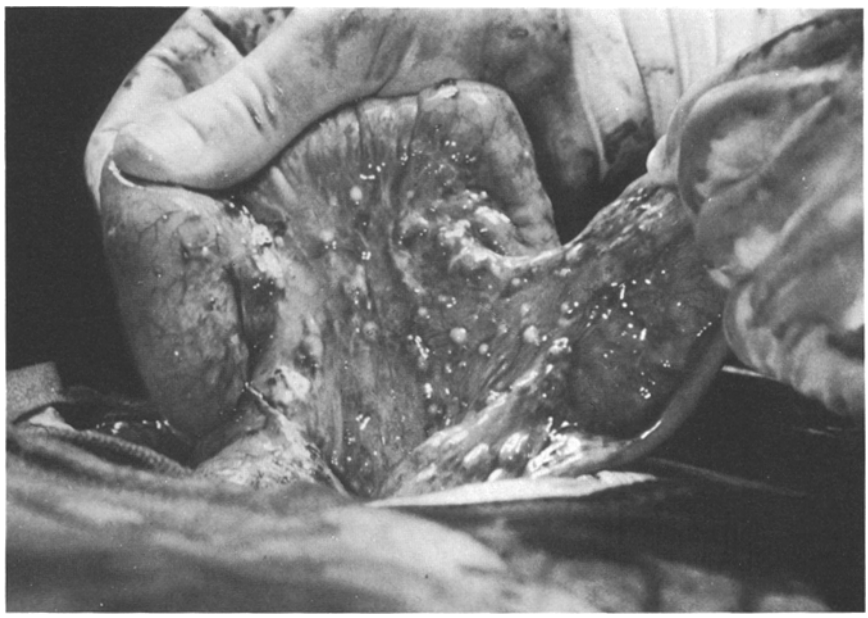

Fig. 3. The appearance of the mesentery at second laparotomy in April 1976. Note that there are still present numerous nodules of variable size, but really large nodules have not been seen

The patient was seen at intervals until April 1976 when a second operation was undertaken in order to remove the uterus. Alerted by the previous operation 4 months ago, particular attention was paid to the appearance of the peritoneal cavity (Fig. 3). Although it was still studded extensively with leiomyomatous nodules involving the bowel, the omentum, the capsule of the liver, the anterior surface of the uterus, the broad ligaments, and the tubes, the nodules had distinctly regressed in size (Fig. 4). There were, however, present numerous adhesions which bound the descending sigmoid firmly to the posterior aspect of the uterus, so that the hysterectomy originally contemplated could not be performed. Instead both tubes were excised, as was the right ovary, which was distended by a cystic mass. This subsequently turned out to be a simple cyst and will not be discussed further.

Pathology

In the first biopsy specimen submitted on December 1, 1975 four specimens were received. They consisted of tissue fragments which contained multiple nodules of variable size, the smallest about 0.3 cm in diameter, the largest about 0.8 cm in diameter (Figs. 2, 4). There was, however, also received a separate single nodule measuring 2 cm × 1 cm × 1 cm. All the nodules felt rather hard and their cut surfaces showed well circumscribed outlines with a whitish and, occasionally, swirling appearance. On microscopic examination all the specimens had essentially the same appearance, which led to a diagnosis of multiple leiomyomatosis. The nodules consisted of whorls and clusters of large cells with pink cytoplasm suggesting the appearance of smooth muscle cells.

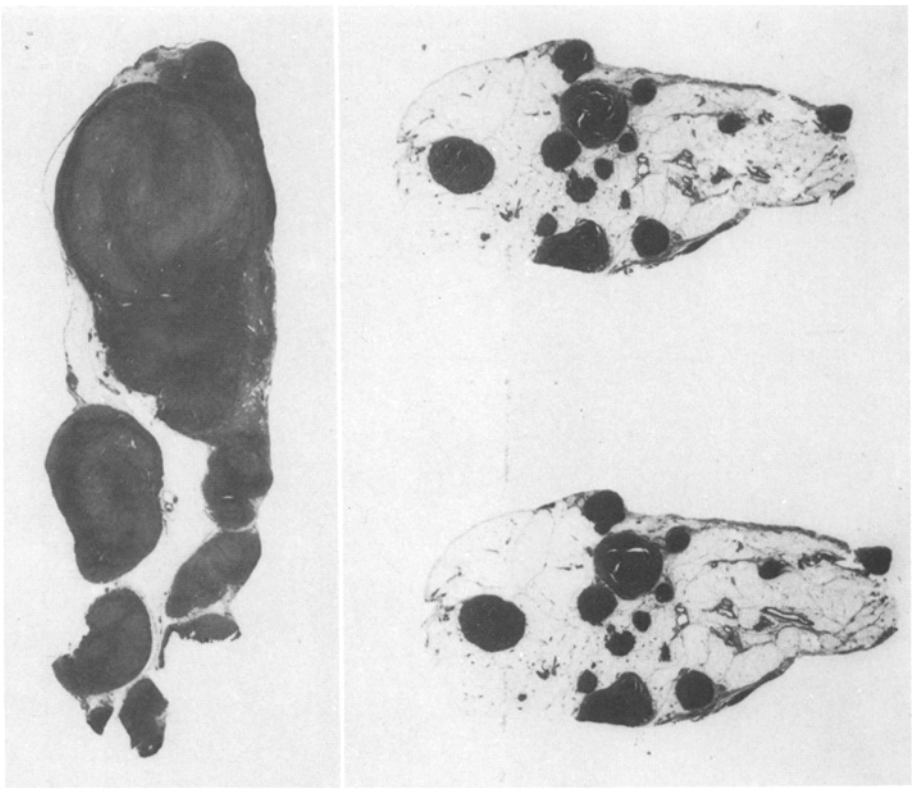

Fig. 4. A low power photomicrograph to show the marked diminution in the size of the nodules over a period of about four months. The specimen on the left was taken at the first, the one on the right at the second biopsy. The histological slides from both specimens were photographed side by side (identical magnification), × 3.5

They were uniform and there was no histological evidence of malignancy in the form of pleomorphism, bizarre cells, or excessive numbers of mitotic figures (Fig. 5). There was, however, an additional finding of interest present which can be summarized as "decidual change" of the connective tissue cells. These cells were large and somewhat foamy or vacuolated (Fig. 6). They were either single or in groups, found either by themselves in the connective tissue, often in the vicinity of blood vessels, or interspersed between muscle fibers. No constant arrangement could be made out and no constant relationship between muscle fibers and decidual cells was discerned. The decidual cells were fairly abundant in some areas, but completely missing in others.

Particular attention was paid to the relation of the leiomyomatous nodules to adjacent vessels. Again no distinct relationship could be seen. There were nodules which seemed to be entirely unrelated to any of the larger blood vessels present; conversely, there were vessels which had no relation whatever to the nodules (Fig. 7). Occasionally, however, a vessel could be found, one of whose walls seemed to be at least topographically related to the tumor nodule. In

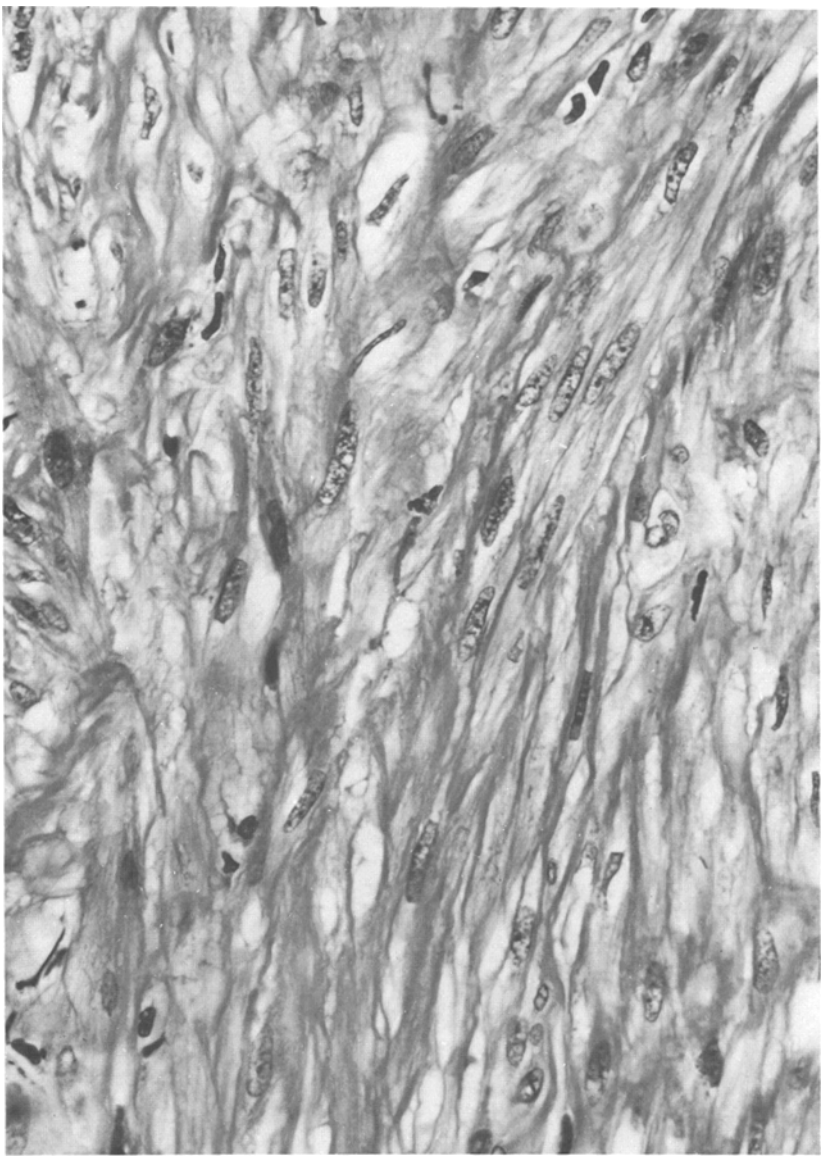

Fig. 5. Photomicrograph of an omental leiomyomatous nodule taken at the first biopsy (Dec. 1975), to show the characteristic histological appearance. Please compare this picture with Figure 1 and with Figure 8. 10% buffered formalin, 6 μ, H & E, ×510

the two-dimensional sections the picture thus seen was that of a nodule closely adjacent to one wall of the vessel, whereas the other wall was completely free of tumor. Nowhere was there seen a picture in which there was a consistent and/or a concentric involvement of the vessel wall by the tumor, indicating the uninterrupted transition of the one into the other. Even when a vessel seemed completely embedded in the tumor, on close examination an intervening slit-like "free" area was still present to show that the smooth of the vessel and of the tumor nodule were independent of each other.

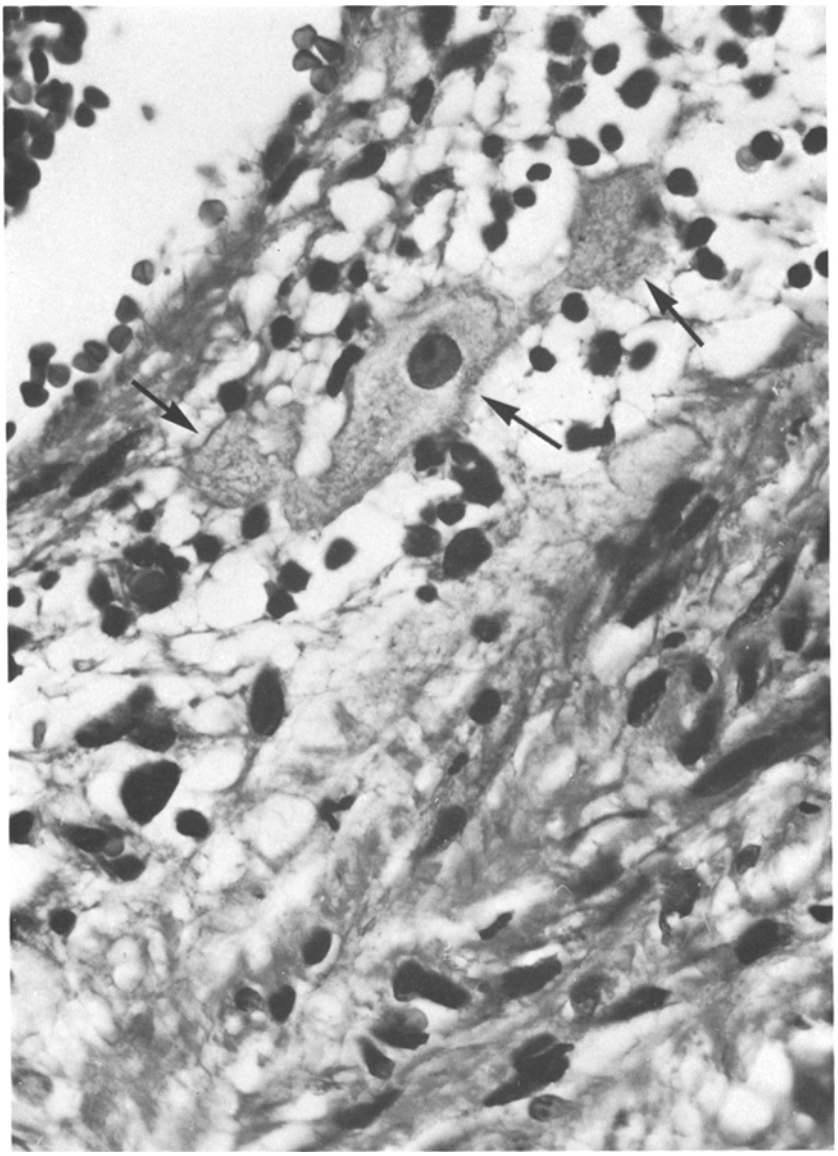

Fig. 6. Photomicrograph of omental biopsy with leiomyomatous nodules (Bottom left) to show the presence of decidual cells (Arrows). Same specimen as Figure 5. × 800

Another feature of great interest in these sections was the frequently ill-defined outline of the tumor nodules which seemed to fade into the surrounding connective or fatty tissue (Fig. 7). This, in turn, in the transitional areas gave an impression of "unrest" quite different from the more uninvolved areas, with prominent cells having sometimes features suggestive of decidual change, and prominent fibers which merged with the fibers in the tumor. The appearance suggested a "recruitment" of the connective tissue elements for the tumor nodule, and the "unrest" seen was interpreted as the expression of the response

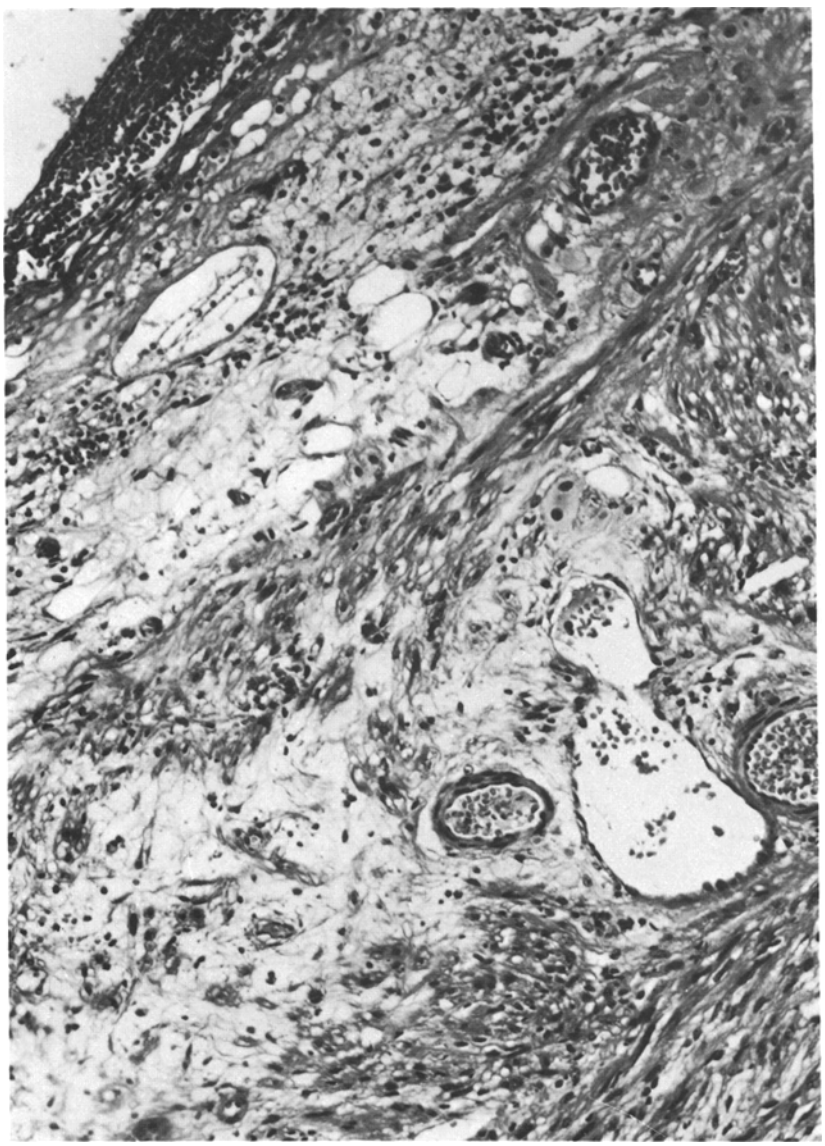

Fig. 7. Photomicrograph to show the relation of an omental leiomyomatous nodule to vessels, and to illustrate the "unrest" of the connective tissue elements suggestive in areas of "recruitment" by the nodule (lower right and left corners). Same specimen as Figures 5 and 6. 10% buffered formalin, 6 μ, H&E, × 190

of the connective tissue to the stimulus which, in its full development, led to the formation of the full-blown leiomyomatous nodules. No explanation for the localized nature of these changes, however, could be derived from these histological studies.

The second biopsy specimens removed at laparotomy in April 1976 showed a gross appearance similar to that seen in the earlier samples, except that a very striking reduction in the size of nodules was now apparent (Fig. 4). Histologically (Figs. 8, 9) also this reduction in cell size could be quite easily

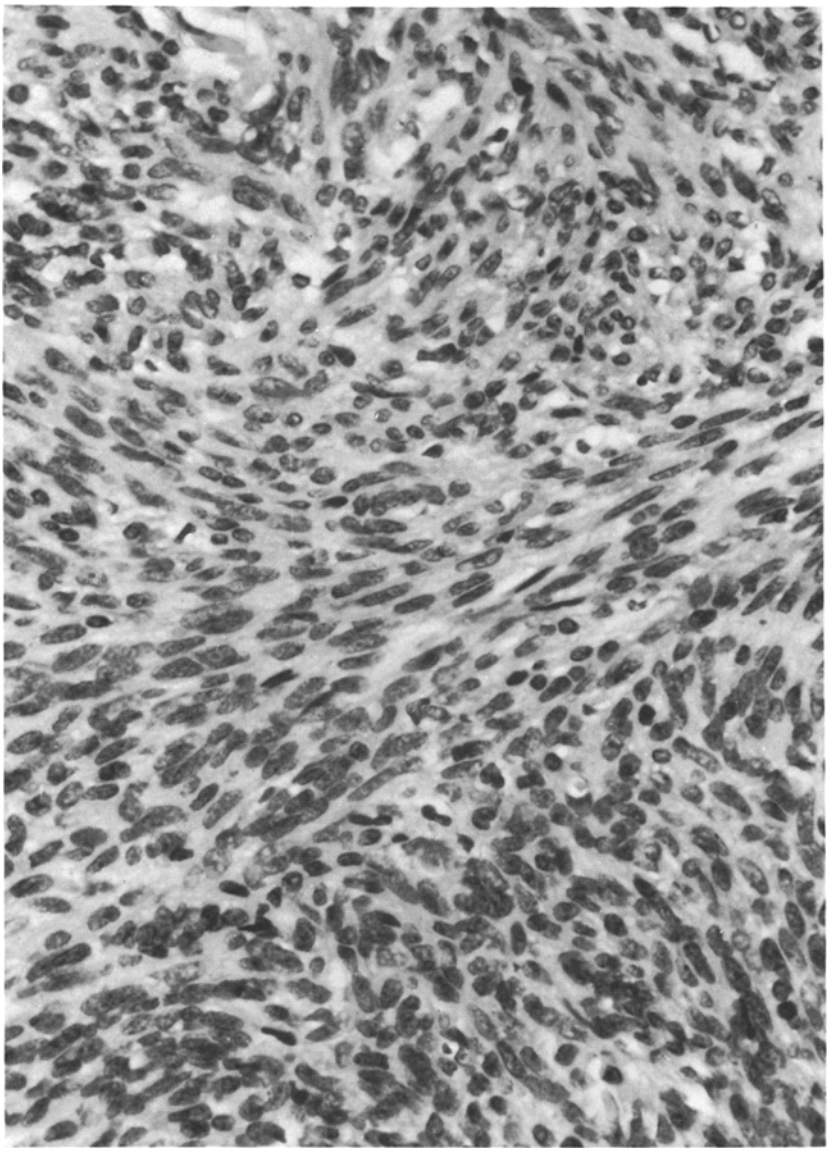

Fig. 8. Photomicrograph of involuting peritoneal nodule taken at second biopsy (April 1976). Compare this picture with Figures 1 and 5, and note the marked attenuation of the cytoplasm, the decrease in size of the nuclei, and the consequent seemingly increased cellularity of the nodule. This histological appearance accounts for the naked-eye decrease in size of the nodules shown in Figure 4. 10% buffered formalin, 6 μ, H & E, ×510

seen. Judging by the number of nuclei, the number of cells did not seem to have decreased, but the cells were smaller with less cytoplasm, with the result that the tumor nodules now appeared considerably more cellular and hence somewhat more alarming. Close examination, however, showed the cells to be quite uniform, no obvious nucleoli were seen, and nowhere was there any atypical cellular change or an increase in the number of mitotic figures; in most instances the nodules were quite sharply circumscribed without any evidence of invasion or extension. The cytoplasm was reduced to barely visible

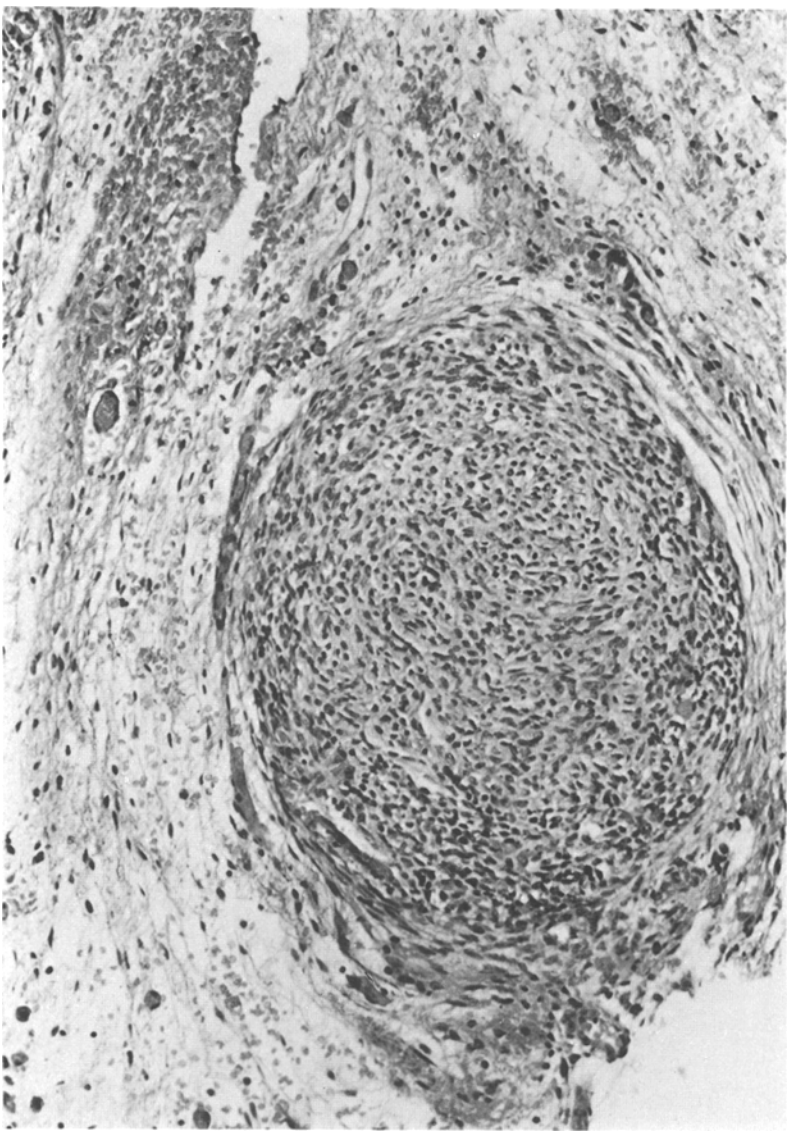

Fig. 9. A low power photomicrograph of another such nodule to show its small size, fairly sharp outline, seemingly increased cellularity, and the "settled" appearance of the surrounding tissue. It would be difficult at this stage to make a diagnosis of "leiomyoma". 10% buffered formalin, 6 μ, H & E, ×160

rims, so that essentially the tumors appeared to consist almost of naked, uniform nuclei distinctly reduced in size. No decidual cells were seen, and the "unrest" of the connective tissue described earlier on was no longer present (Fig. 9). Special stains did not show a significant increase in the amount of connective tissue in the nodules. The prominence of connective tissue fibers in some areas was attributed to the general reduction in size of the tumor nodules. It could not be classified as "fibrosis" of the tumors. In areas it would have been difficult to make now a diagnosis of leiomyomatosis and the tumor, presumably, would have been considered almost entirely "fibrocellular".

Comment

There appear to have been only eight acceptable cases of disseminated peritoneal leiomyomatosis described so far (Wilson and Peale, 1952; Crosland, 1973; Taubert et al., 1975; Parmley et al., 1975), if the case briefly referred to by Hüssy (1939, 1940) is included. The latter, however, considered this condition to be sarcomatous, and "saved" his patient by intense radiotherapy. The case reported by Massé, Dax and Carles (1953), and accepted by Taubert et al. (1975), may or may not belong to the category outlined here, since they described an ovarian leiomyoma presenting at operation numerous "granulations" of the pelvic peritoneum. The small number of reported cases, however, is not necessarily an indication of the true incidence of this condition. Single cases may not always be reported. All the cases described so far have been discovered incidentally at laparotomy undertaken for other reasons. Since there is no characteristic clinical picture associated with this condition, it is conceivable that some unoperated instances are simply not discovered. Had this been the case, however, it would be expected that, in view of the frequency with which laparotomies are nowadays performed, more instances of disseminated peritoneal leiomyomatosis would by now have been reported. The disorder, therefore, appears to be uncommon, is not well known, and certainly not well understood.

According to Stout et al. (1963) peritoneal leiomyomas – very rare tumors – can occur in men, but in these instances they are large and solitary, and may be malignant. The diffuse occurrence of multiple, mostly small, leiomyomas studding the peritoneal cavity, only occasionally accompanied also by a somewhat larger mass, has so far only been described in women. Leiomyomas of the uterus had been present at one time or another in most of the patients in this category examined, but there was little evidence that the nodules in the peritoneum were causally associated with these uterine leiomyomas. The explanation of "seeding" or implantation from a preexisting leiomyoma in these instances is difficult to accept. Already Crosland (1973) dismissed this possibility, since he noted that in most instances the "parent" leiomyomas were quite clearly not on the surface of the uterus where they might have led to implantation metastases. In the case of Willson and Peale (1952) a sub-total hysterectomy had been performed 11 years before another laparotomy for unrelated reasons showed disseminated leiomyomatosis peritonealis. It is thus more likely that the presence of leiomyomas in the uterus is an expression of an underlying abnormality which, on occasion, can also lead to the development of disseminated leiomyomas in the peritoneum. This point needs to be stressed here, since Taubert et al. (1975), in the sub-title to their paper on leiomyomatosis peritonealis disseminata, state this to be "an unusual complication of genital leiomyomata". It is very questionable whether disseminated leiomyomatosis peritonealis should be considered a complication of genital leiomyomata rather than the simultaneous or delayed manifestation of an underlying pathological condition giving rise to both.

An indication of the nature of this condition can be gained not only from the exclusive occurrence of disseminated leiomyomatosis in women, but also from the fact that six of the nine reported cases so far were associated with pregnancy and some, including the case presented here, showed a typical decidual

reaction in or around the leiomyomatous nodules. Moreover, in the case of Willson and Peale (1952) the disseminated leiomyomatosis was associated with a granulosa-cell tumor of the ovary. These authors leave no doubt about this association. There are thus seven women in whom endocrine factors seem to have been intimately associated with the development of this condition. Whether the thyroid disturbance of the patient described here has in any way contributed to the abnormal endocrine environment against whose background disseminated peritoneal leiomyomatosis appears to develop is doubtful. Manifest thyroid or other endocrine disturbances have not been described in the other patients. The association with pregnancy and, at a later age, with an ovarian tumor prone to endocrine activity, however, strongly suggests that there is a link between sex hormones and the development of disseminated leiomyomatosis peritonealis.

There is another argument in favour of this assumption, based on the many experiments in which leiomyomas of the genital tract have been produced in animals, mainly guinea pigs (Nelson, 1937, 1939; Lipschutz et al., 1938; Lipschutz and Vargas, 1941; Perloff and Kuzrok, 1941; Lipschutz, 1950). That the experimental, as well as the human uterine leiomyomas can be influenced by hormonal factors is well known. A more explicit corollary to the condition discussed here can, however, be found in the extensive experiments of Lipschutz and his associates (Lipschutz et al., 1938; Lipschutz and Vargas, 1941; Lipschutz, 1950), who succeeded in producing by suitable endocrine manipulation disseminated leiomyomas in the peritoneal cavity. In fact Figure 10 of Lipschutz's (1950) monograph closely resembles the appearance seen in our patient (Fig. 3). It is unfortunate that the work of Lipschutz has been dismissed as not representing the formation of true leiomyomas (Editorial, 1946). This is not surprising if one considers that Iglesias and Lipschutz (1946) at one time spoke of an "abdominal fibrous reaction". Lipschutz (1950) blames himself for this misunderstanding, since he was anxious to underline the similarity of his experimental findings to the "fibroids" seen by gynecologists and pathologists. It would be important and rewarding to reinvestigate Lipschutz's (1950) older findings and to demonstrate the leiomyomatous nature of his "fibromyoma" nodules.

This point raises another question concerning the etiology of this disorder. In the most recent paper on the subject Parmley et al. (1975) suggested as a synonym for "leiomyomatosis peritonealis disseminata" the term "disseminated fibrosing deciduosis". They maintained that essentially the leiomyomatous nodules seen were foci of a decidual reaction elicited by the pregnancy, in which a marked "fibrocytic" response may lead to the development of a "pseudoleiomyomatous pattern. This fibrocytic process undoubtedly explains the developmental sequence of the majority of the reported cases of the entity 'leiomyomatosis peritonealis disseminata'". The authors even go so far as to say that "the nature of the stimulus which initiates the replacement of decidua by fibrous tissue is undoubtedly similar to that noted at other sites of repair and replacement". The case presented here does not bear out these suggestions. Although there was present a decidual reaction in the specimens removed at the first biopsy, fibrous tissue development was not a very striking feature, and by all light microscopic criteria the leiomyomatous character of the nodules was quite apparent. If these "deciduous" nodules were replaced by fibrous

tissue or the tumors represented a "fibrosis" of the decidual foci, one might have expected that this process would become more accentuated as time progressed, so that in the end the fibrous tissue reaction would be the predominant feature. This was not the case in the nodules studied at the second laparotomy in the case presented here. On the contrary, although the decidual reaction had completely disappeared, a true and excessive "fibrosis" was not seen. The nodules had only become smaller and seemingly more cellular. The cellularity of connective tissue and of scars, in general, tends to decrease with age. Here, however, the cellularity of the nodules had seemingly increased largely due to a shrinkage of the previously well developed smooth muscle cells. The evidence that leiomyomatosis peritonealis disseminata is, as Parmley et al. (1975) maintain, "the result of a benign fibrous replacement of decidual tissue" should, therefore, not be accepted as proved. There is, in fact, no evidence that the decidual reaction, which is such a common occurrence in pregnancy, is indeed causally related to the development of peritoneal leiomyomas of the type described here. It is again quite possible that the leiomyomatous change merely represents a "metaplasia" occurring simultaneously with the change described as "decidual", and perhaps due to the same hormonal stimuli. The frequency of decidual reactions, and the rarity of the leiomyomatous transformation, however, raise the possibility that an additional factor may be required to produce the latter. Since the development of multiple leiomyomatous nodules in the peritoneal cavity may have its counterpart in the experiments of Lipschutz and associates (1950), it would be highly desirable to investigate the development and regression of these experimental nodules by modern cytological and ultrastructural means, so as to establish the precise nature of this condition.

Finally it should be stressed that disseminated leiomyomatosis peritonealis appears to be a benign condition. None of the patients reported seemed to have died of it; in those instances in which a follow-up report had been published, the patients appear to have done well; and now morphological regression has been histologically demonstrated. Since in the case presented here the regression took place after the termination of pregnancy, without the additional removal of the ovaries as a possible source of hormones perhaps contributing to the maintenance of this condition, one may question the necessity for any treatment. Perhaps this condition is merely one of the rarer and more dramatic expressions of the widespread changes which take place in the body under the influence of pregnancy. The simultaneous presence of the decidual reaction would tend to point in this direction. It would be well to keep this possibility in mind, since the risk of mis-diagnosing this condition as malignant may have deleterious consequences for the patient.

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Note Added in Proof. An additional instance of leiomyomatosis peritonealis disseminata has been depicted by Ackermann, L.V., and Rosai, J., in their "Surgical Pathology", the C.V. Mosby Co., St. Louis, 1974, p. 817. Unfortunately no clinical details of this case are given.