An Autopsy Case of von Recklinghausen's Disease with Malignant Transformation

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Neurofibromatosis (von Recklinghausen's disease) is fairly common disease and is characterized by the multiple cutaneous tumors, the so-called mollusca fibrosa. This is regarded to be one variety of misdevelopment of the entire nervous system or any of its component parts, with a strong hereditary background. The origin and the true nature of the tumor, however, are still preserved in discussion.

Not uncommonly, malignant degeneration takes place and the disease progresses in fatal fashion. We recently autopsied a woman who had characteristic tumors of the skin, with malignant change at the right knee region.

CLINICAL COURSE

A woman, aged 39, had noted the gradual appearence of multiple soft tumors, scattered over her forearms, lower extremities and trunk since the age of 13 years. At that time a diagnosis of von Recklinghausen's disease was made. These cutaneous nodules steadily increased in number and size with increasing age. About two years prior to the admission, the patient began to have localized pain at the right thigh and disturbances in the gait. Flexion contracture of the hip and knee joint on the right side gradually appeared and the pain increased in intensity. As the medical treatement was unsuccessful, on November 22, 1960, she was admitted to the orthopedic clinic of Yamaguchi Medi-

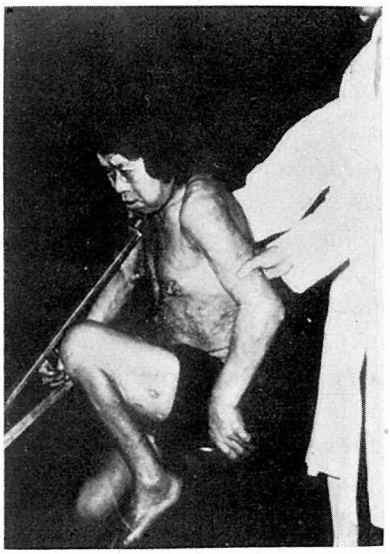

Fig. 1. Multiple cutaneous tumors and flexion contracture of the hip and knee joint.

cal School Hospital.

Physical examination revealed slightly emaciated woman with innumerable cutaneous nodules of various sizes scattered over the surface of her trunk and limbs (Fig. 1). These tumors with characteristic consistency were well circumscribed and covered by the pigmented skin. Skeletal examination revealed mild scoliosis sinistra and rounded back. The right hip and knee joints were both in flexion contracture, making an angle of 60 and 20 degrees respectively. Although flexion of these joints was complete, further extension was markedly restricted. X-ray examination of the right knee area revealed deformity of the right knee joint and slight atrophy of the bones, but destruction of the the bone by the tumor was not exhibited (Fig. 2). The chest film was normal. Her blood pressure was 120/70. The electrocardiogram was within normal limits. Hematological examination showed slight degree of normocytic normochromic anemia. Blood chemistry demonstrated slight depletion of her general condition. Adrenocortical function test was normal. On both sides, ankle reflex was hyperactive and patellal and ankle clonuses were noted, but pathological reflexes were not elicited. There was decrease of sensations of touch and pain in the right foot. No members of her family were similarly affected.

Under intravenous labonal anesthesia, manipulation of the right hip and knee joint was performed, which resulted in making extension of 110 degrees of the hip joint and that of 70 degrees of the knee joint possible.

Fig. 2. X-ray film of the right knee regin.

About 8 months prior to her death, amputation of the m. sartorius and m. rectis femoris and that of m. quadriceps femoris, m. semimembranosus and m. semitendinosus were performed so as to remove the muscular contracture of the right hip and knee joint. On that occasion, two tumors of egg size were observed along the tibial nerve, and the tibial and fibral nerves were both compressed by the tumors and was atrophic. Histological examination of one of these tumors revealed neurofibroma.

After the operation, the right lower extremity was placed in traction by Kirschner's wire. Approximately 3 months after the operation, the posterior surface of the right knee gradually came to be swollen and its central portion was occupied by soft tumor mass (Fig. 3). Biopsy taken from the tumor showed malignant change

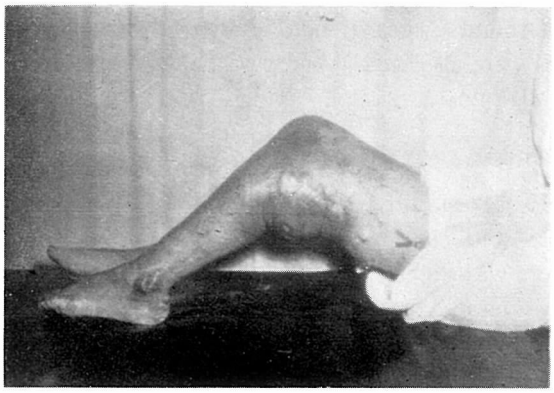

Fig. 3. Remarkable swelling of the right thigh and knee region.

of neurofibroma with great cellularity and abundant mitosis. Afterward, the portion from which the biopsy specimen was taken became widely ulcerated and bleeded easily. The tumor mass rapidly increased in size and her general condition gradually deteriorated and she died on July 7, 1963.

Autopsy Findings;

A postmortem examination was performed three hours after death. The body was an emaciated woman, aged 40. The most peculiar finding was multiple soft cutaneous tumors which varied in size and shape and irregularly distributed over the skin. Most tumors were covered by the pigmented skin. The thigh and knee region on the right showed remarkable swelling and the size of the thigh was approximately three times larger than that of the left side. This swollen part of the knee was found to be occupied by firm tumor mass with its posterior surface ulcerated. Cut surface of this tumor was white in color and rather ill defined. The tumor mass was too large to detect the nerve trunks within it.

There was pitting edema of the right lower extremity.

The heart was 250gm. in weight and the myocardium was brownish in color. There was fibrous adhesion bilaterally over all the lobe of the lung. Section through the lungs revealed two pieces of sharply circumscribed, pear sized tumor of soft consistency at the apex of the right side. Both kidneys weighed 160gm. and intact. The liver was 1000 gm. in weight and the left lobe was remarkably atrophic. On the mucosal surface of the duodenum, pear sized nodules were found and the same sized nodules with soft consistecy were also scattered on the serosal surface of the jejunum. Though the appendix was almost the same size as normal, its wall was thickened and moderately firm in consistency. The thyroid gland was normal in size, but sections revealed brownish, rounded shaped nodules which varied from less than a mm. to 5mm. in diameter. The adrenals showed no signifi-

cant gross abnormalities. Thumb sized ovarial cyst which contained straw colored mucinous fluid was found at the left side. Polypoid protrusion of the endometrium and cervical polyps were also seen. Autopsy of the central nervous system was not carried out.

Microscopical Findings;

Cutaneous tumors were located intradermally or in the subcutaneous tissue and most of them were well circumscribed but not encapsulated (Fig. 4). The skin overlying the tumors was slightiy atrophic and often pigmented in varying intensity. These tumors were composed of the bundles of elongated cells with wavy arrangement of the fibrils, which is regarded as characteristic of neurofibroma (Fig. 5).

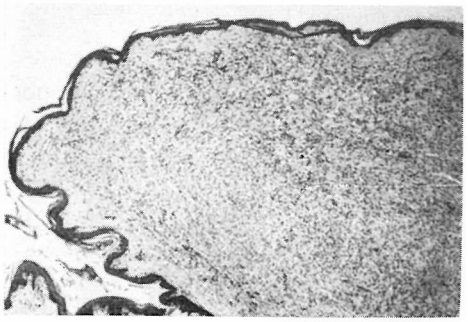

Fig. 4. Cutaneous tumor. H. E. × 40

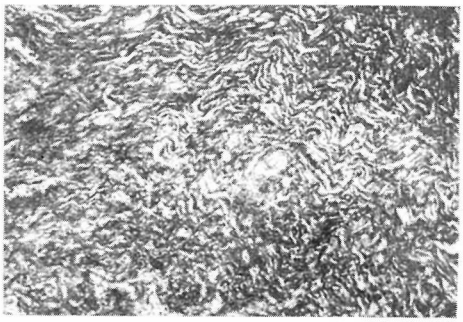

Fig. 5. Wavy arrangement of the fibrils. Van Gieson. × 100

Occasionally, these collagenous fibers lay in loose strands, because of mucoid degeneration of the collagen, and showed the tendency to form eddies and whorls. Subcutaneously proliferated neurofibromatous tissue was occasionally arranged in concentric fashion around the sweat and sebaceous glands (Fig. 6). Palisade appearence of the nuclei was scarcely visible. These fibrils stained pink with hematoxylin and eosin, reddish with van Gieson's connective tissue staining and blue with Azan-Marroly's. The nerve fibers were not demonstrated in the cutaneous tumors by these staining methods.

The tumors of the small intestine, which were located in the muscular layer, showed almost the same histological features as the cutaneous tumor. At the appendix, the tumor was poorly circumscribed and because of proliferation of the tumor tissue in the mucosal layer, the lumen was almost obliterated (Fig. 7).

The tumor at the apex of the lung showed interesting histological appearence. Many empty irregularly shaped tubular structures were clearly visible in the neurofibromatous pattern (Fig. 8). This appearence was, at first sight, similar to that of fibroadenoma of the breast. Most of these tubular structures were partly lined with simple cuboidal or columnar epithelium, which occasionally ciliated (Fig. 9). In

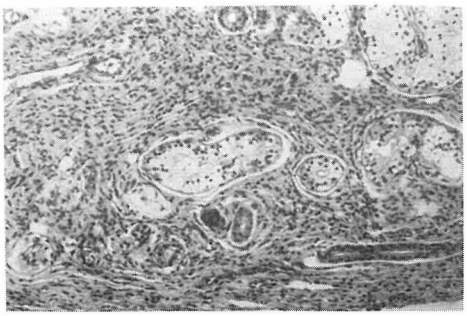

Fig. 6. The sebaceous and sweat glands are surrounded by the neurofibromatous tissue. H. E. × 100

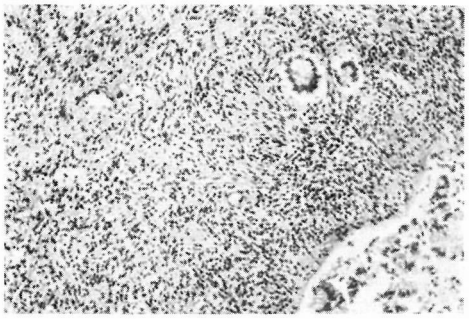

Fig. 7. Neurofibroma proliferated in the muosal layer of the appendix. H. E. × 100

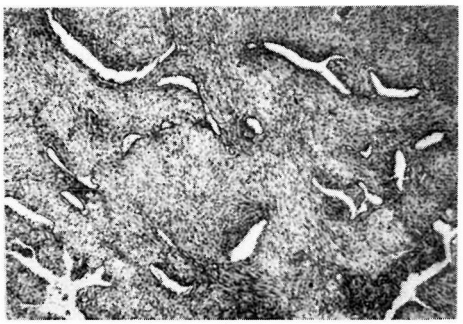

Fig. 8. Tubular structure in the neurofibroma of the lung. H. E. × 40

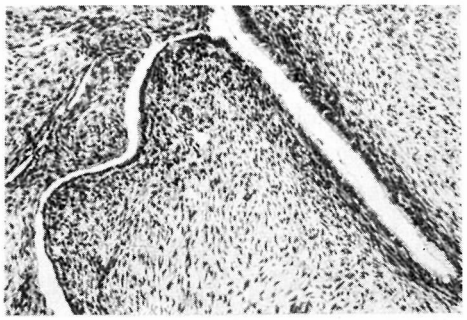

Fig. 9. Epithelial arrangement. H. E. × 100

some area, especially at the periphery of the tumor, however, such epithelium was absent and only thin endothelial arrangement was seen. In some part, the basement membrane was distinctly visible under the epithelium by silver impregnation method. At the periphery of the tumor, neurofibromatous tissue was revealed to proliferate into the alveolar walls and the alveolar spaces were irregularly compressed and transformed into tubular structures (Fig. 10). Therefore, these epithelial arrangement was interpreted to be originated not from the tumor elements but from either the bronchial epithelium or the alveolar epithelial cells. In these tumors, mucoid degeneration of the collagen was remarkable, but malignant histological appearences, such as nuclear pleomorphism and abundant mitotic figures were not observed. Staining reaction to the various methods was almost the same as shown in the cutaneous tumors.

The tumor mass of the right knee region was highly cellular and composed of fasciculated spindle shaped cell which interlaced (Fig. 11). The nuclei were hyperchromatic and pleomorphic with abundant mitotic figures (Fig. 12). In some area, palisade like appearence of the nuclei and mucoid degeneration of the collagen

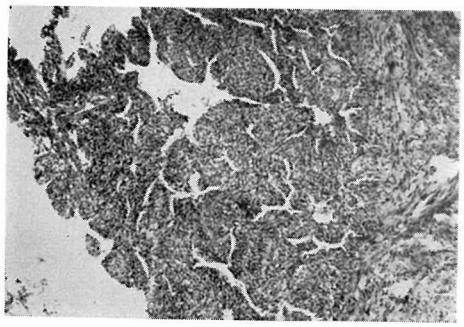

Fig. 10. At the periphery of the tumor, alveolar spaces are irregularly compressed by the proliferated tumor tissue. H. E. × 40

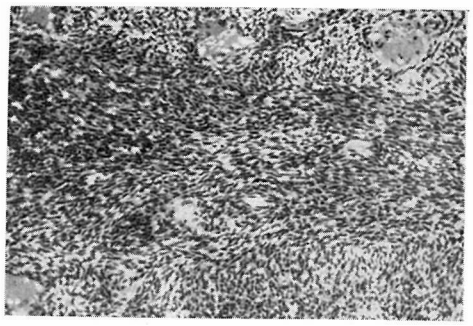

Fig. 11. High cellularity and fasciculated bundles of spindle shaped cells. H. E. × 100

were recognized (Fig. 13), but the general histological structure was similar to that of fibrosarosarcoma or spindle cell sarcoma, and even by the specific staining methods differential diagnosis was hardly possible.

Other histological findings. 1) partial pulmonary atelectasis. 2) congestion and fatty degeneration of the liver cells in the central portion of the lobules, and proliferation of the connective tissue in the left lobe. 3) struma colloides bilateralis. 4)

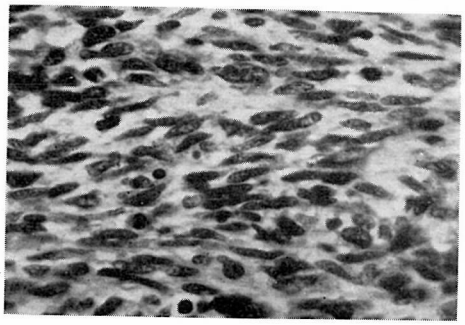

Fig. 12. Pleomorphism and abundant mitotic figures. H. E. × 400

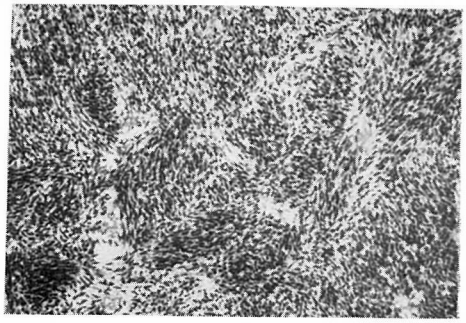

Fig. 13. Palisade like appeareace of the nuclei. H. E. × 100

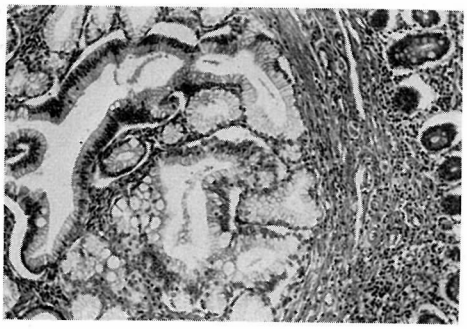

Fig. 14. Adenoma in the duodenum. H. E. × 100

erosio portionis with formation of Nabothian follicles. 5) cystic dilatation of the uterine glands. 6) adenoma in the muscular layer of the duodenum (Fig. 14).

COMMENT

Generalized neurofibromatosis was first described as the multiple tumors arising from the endoneurium by von Recklinghausen in 1882, and it has since been called von Recklinghausen's disease. He originally regarded the tumor as derived from the mature connective tissue of the nerves. Verocay, in 1910, suggested that the cells of the tumor were immature cells of the sheath of Schwann and used the name "neurinoma". Ever since, two schools of thought have developed regarding to the origin and nature of these tumors. Among recent writers, some (Murray and Stout)[1] subscribe to Verocay's view, but others (Tarlov)[2] still adhere to the view that the tumors develope from the perineural connective tissue. Many more recent authors, however, feel that probably both ectodermal schwannian sheath cells and perineural connective tissue cells participate in the formation of the tumors.[3] McNairy and Montogomery[3] clearly demonstrated the nerve fibers in the tumor in 12 out of 15 cases of von Recklinghausen's disease by using Bodian's method of staining. The presence of nerve fibers in the majority of neurofibroma would be supportive evidence that these lesions are true neurofibromatous structures which arise from the peripheral nerves and their supporting structures. It is unfortunate that the schwannian cell and endoneural fibroblast cannot be distinguished by present histologic methods. Furthermore, as the schwannian cells also produce reticulum fibers[4] and collagen[5], the presence of these structures in neurofibroma does not decide the issue. At present, it would be convenient to understand the varied histological appearence of the tumor, if we adopt the thought that both schwannian element and the perineural connective tissue participate in the formation of the tumor.

In this case, most tumors of the skin, small intestine and lung were composed of wavy fibrils of collagen and occasionally showed the tendency to form eddies and whorls. With special staining methods, such as Van Gieson, Mallory-Azan and silver impregnation method, it was hardly possible to detect the nerve fibers in the tumor and to decide the origin of the tumor.

Malignant degeneration in neurofibromatosis is not uncommon. Hosoi,[6] in 1931, collecting 65 instances of malignant degeneration reported in the literatures, concluded that the malignant change took place in about 13 per cent of all cases of neurofibromatosis. Up to 1958, approximately 19 cases of malignant change in von Recklinghausen's disease were reported in Japan.[7] As far as the authors collected the autopsied cases from "Annual of Pathological Autopsy Cases in Japan" published in recent four years (1958–1961), there were 22 instances of von Recklinghausen's disease and malignant transformation was found in four cases. This

represents 22 per cent of all autopsied cases of von Recklinghausen's disease during recent four years in Japan and this percentage is much higher than 13 per cent reported by Hosoi. These figures, however, may not be justified, as Lever[8] pointed out, since in neurofibromatosis, as in other uncommon diseases, exceptional cases are autopsied or reported more often than ordinary ones.

Malignant degeneration can occur anywhere without close relation to the stadium of the disease[9], but according to Hosoi, it occurred most frequently in the large nerve trunks. Ringertz and Eherner[10] also pointed out that it took place most frequently in the deeply placed nerve trunks, especially those of the lower extremities, and rarely occurred in the neck, thorax and viscera. But special cases in which sarcomatous change occurred in the uncommon places or organs, such as the urinary bladder[11] and the jejunum[12] are also reported. In general, malignant transformatiom of the neurofibromas of the skin is regarded to be rare. As is similar to the case reported by Ross,[11] malignant change in this case took place shortly after the operative interference, and the tumor began to grow rapidly and recurred locally. Therefore, operative procedure to the tumor or to its neighbourhood may play some significant roles to the sarcomatous transformation of neurofibromas.

Clinically, malignant degeneration is suggested by a sudden increase in the growth rate of the tumor and by the appearence of the recurrent lesion.[13] Histologically, however, it is difficult to decide whether malignant neurofibroma is the primary or secondarilly degnerated one from long existed neurofibroma. Most malignant tumors in neurofibromatosis appear like ordinary fibrosarcoma and give no evidence of their origin from neurofibroma. Though histological picture in this case was similar to that of fibrosarcoma or spindle cell sarcoma, in some area, neurofibromatous pattern was still preserved, such as wavy arrangement of the collagen fibrils and palisade like appearence of the nuclei.

About the etiology of von Recklinghausen's disease nothing is definitely known, but this disease is generally regarded to be congenital and occasionally familiar. In this case, however, no hereditary relationship was demonstrared. Additional stigmata such as café au lait spots, bone defect related to the tumor and atrophic change of the skin, or other congenital anormalies such as spina bifida, hypospadia and endocrine disturbance were not associated. Not infrequetly neurofibromatosis is reported to be complicated with the involvement of the central nervous system.[14] Though, in the absence of necropsy of the central nervous system, not many deduction are justified, there was nothing in the physical examination and clinical symptoms to suggest the lesion in the central nervous system.

SUMMARY

An autopsy case of von Recklinghausen's disease (neurofibromatosis) with malignant degeneration at the vicinity of the deeply placed nerve trunk of the right knee

region is reported, and the clinical course of the patient is deseribed.

The histology of the tumor and the views regarding to its origin and sarcomatous degeneration are discussed.

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