Angiofollicular lymph node hyperplasia

By Dan Allan Hansen and B. Kofoed-Nielsen

Angiofollicular lymph node hyperplasia is a relatively rare benign tumour. The first case was published under the heading 'primary subpleural intrapulmonic thymoma' (Crane and Carrigan, 1953). Castleman was the first to recognize the tumour as a unity (Castleman and Towne, 1954; Castleman *et al.*, 1956). The tumour is therefore also known as Castleman's disease. He named the tumour 'localized mediastinal lymph node hyperplasia resembling thymoma'. Until 1957 only tumours localized in the mediastinum were reported. This year three extrathoracic cases have been published, one in the mammary gland, one in the axilla, and one in the supraclavicular region under the diagnosis 'tumourlike proliferation of the lymphoid tissue' (Cohen, 1957). General symptoms in connection with the lesion were mentioned in a case from 1965 (Lee *et al.*, 1965); the signs were fever, anaemia, and hyperglobulinaemia. In a dissertation (Flendrig, 1969) based on 111 cases, the lesion was divided into two different types: a plasma-cell type, 10 per cent; and a hyaline-vascular type 55 per cent. Transitional forms accounted for 35 per cent. General symptoms are almost exclusively seen in the plasma-cell type. The tumour is most often found in the mediastinum. In a statement (Anagnostou and Harrison, 1972) based on 134 cases, the following distribution was found: thorax, 60 per cent; abdomen, 11 per cent; axilla, 4 per cent; and neck, 14 per cent.

Cases of special oto-rhino-laryngologic interest include a tumour in the larynx (Climie *et al.*, 1974) and one in the sublingual region (Schumann, 1966). This paper describes a tumour in the submandibular region in close connection with the submandibular gland, and tumours in the neck are discussed.

Patho-anatomy

Most often the tumour is solitary, but some cases are multiple (Flendrig, 1969), and a few are multifocal. The sizes range from 3 to 16 cm. in diameter, with a weight up to 400 g. Macroscopically the tumour is encapsulated and well demarcated, and the consistency is firm. On the cut surface a nodular structure is seen. There may be cysts, necrosis, bleeding, and calcification. Microscopically, the capsule varies in thickness, and rather large intracapsular vessels are found, especially in the mediastinal tumours. Lymphocytes and plasma cells are common in the capsule.

The hyaline-vascular type consists of small evenly-distributed lymph nodules lying in a richly vascular stroma.

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No distinction between cortical and medullary zones is seen and there are only remnants of the marginal sinus. No marrow sinuses are observed. The follicle centres (Fig. 1) are small and are penetrated by radiating capillaries. The capillary walls are thickened and hyalinized. This results in a concentrically-arranged hyalinized central cell mass (Fig. 2), which somewhat resembles Hassall's corpuscles in the thymus gland, but no keratinization is seen. The follicle centres are surrounded by a sheath of small mature lymphocytes. In the interfollicular stroma a marked vascularity is present (Fig. 3). The proliferating vessels have large, prominent endothelial cells and here and there pronounced perivascular fibrosis and perivascular hyalinization (Fig. 4). The inter-follicular stroma also contains lymphocytes, eosinophilic granulocytes, plasma cells, and

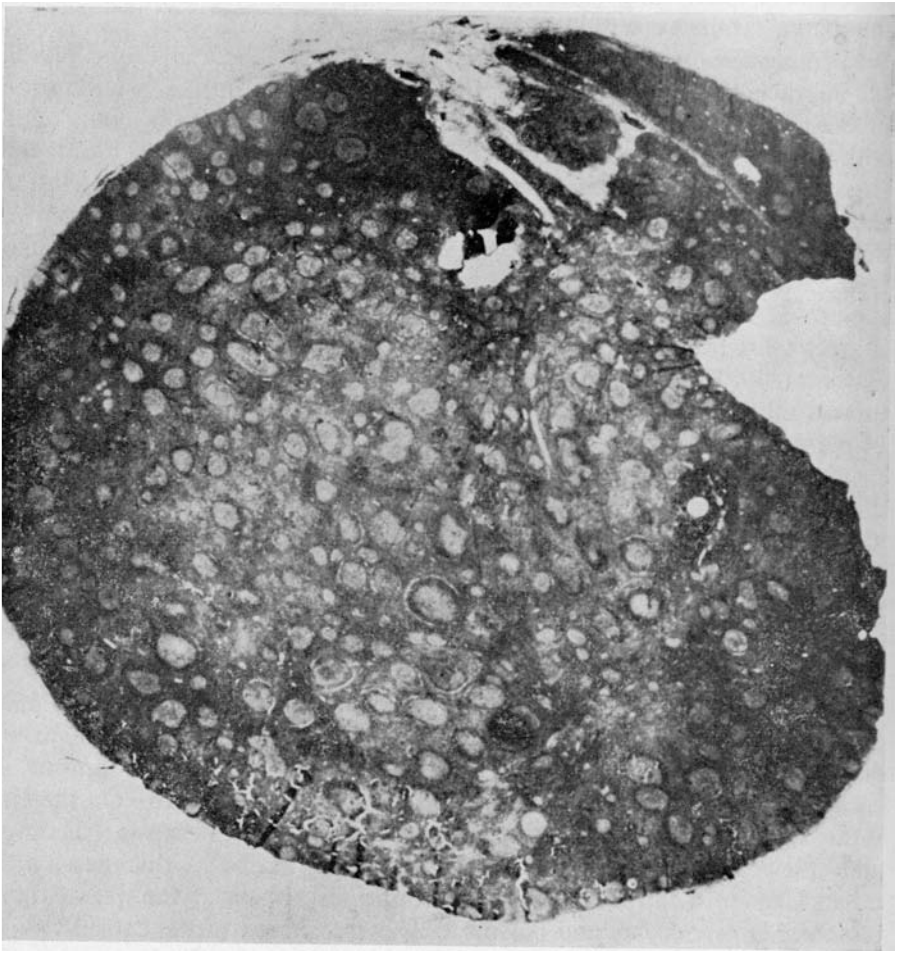


FIG. 1

Low-power appearance. Note the follicles throughout the lesion. (H. and E. ×8.)

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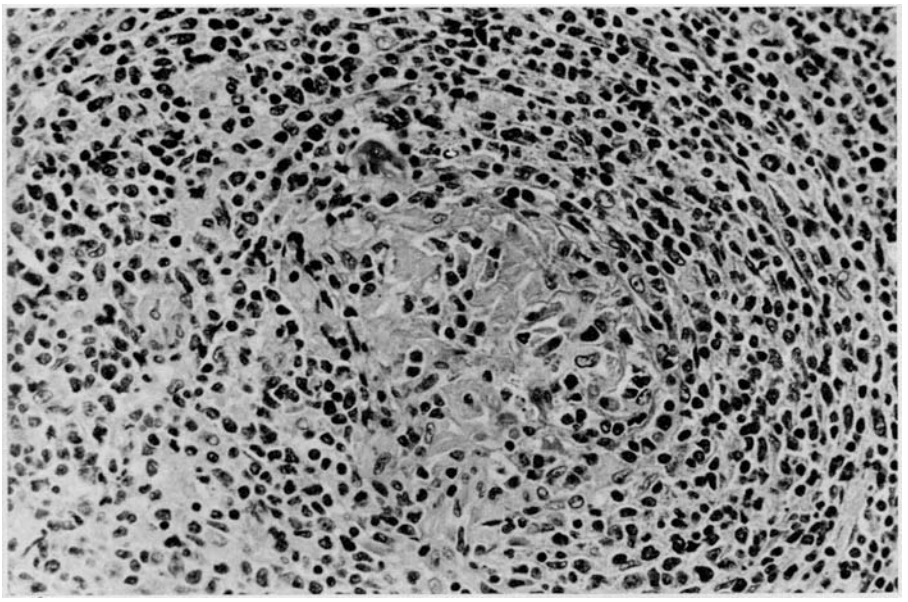


FIG. 2

Follicle centre with fibrous hyalinization. (H. and E. ×400.)

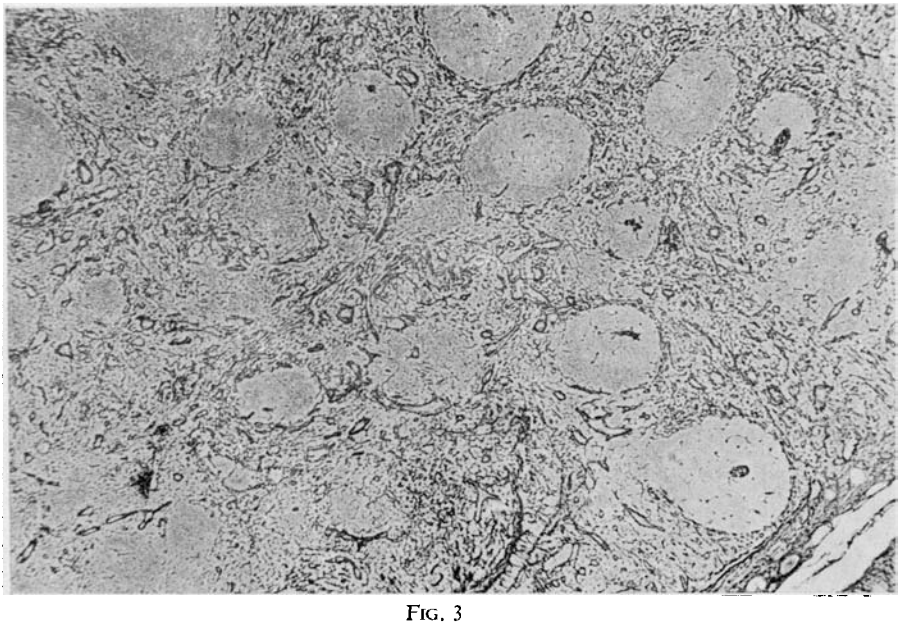


FIG. 3

Low-power view showing follicles throughout the lesion. Note the capillary proliferation in the inter- and intra-follicular tissue. (Reticulin ×64.)

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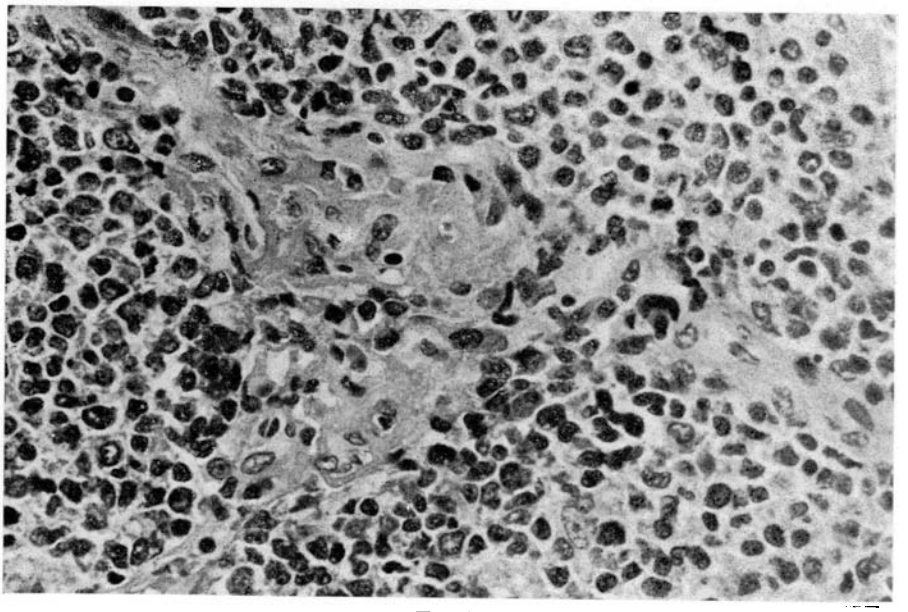


FIG. 4

Interfollicular capillaries with fibrous hyalinization. (H. and E. ×640.)

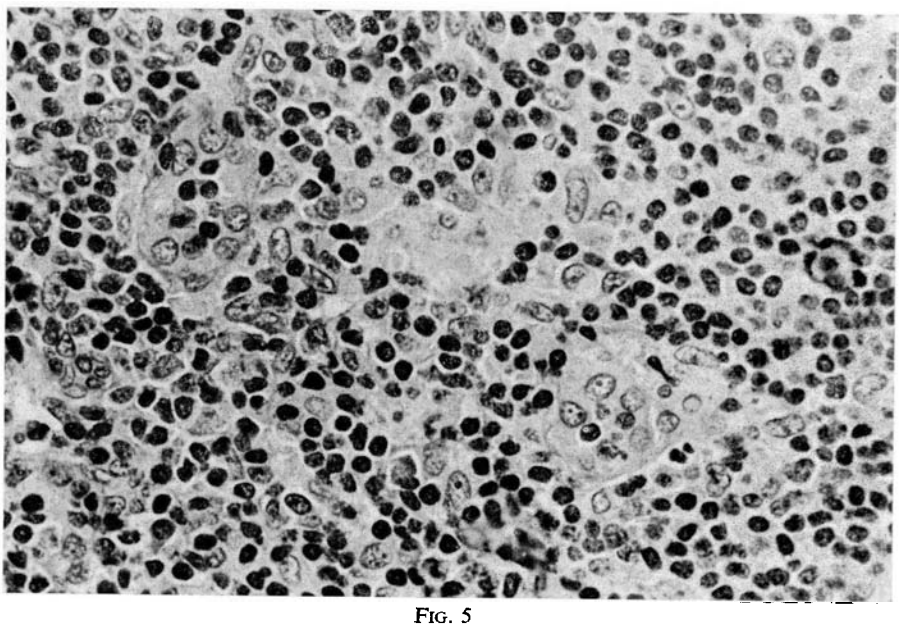


FIG. 5

High-power view of the inter-follicular tissue showing capillaries with large prominent endothelial cells, and large reticular lymphoblasts with prominent nucleoli. (H. and E. ×640.)

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prominent mononuclear cells with large multiple nucleoli, closely resembling the reticular lymphoblasts or basophilic stem cells often seen in association with viral infections and other conditions of lymphoid stimulation (Fig. 5). In the plasma cell type the same picture with evenly-distributed lymph nodules is found, but the follicles are larger with normal bright reaction centres. There is marked intrafollicular vascularization, but there is no proliferation of vessels inside the lymphoid follicles, and in the stroma large dense fields of normal mature plasma cells are found. A large number of tumours are intermediate between the two types described above. Mixed types, made up of areas of both types situated in the same tumour, might also be seen.

Clinical features

The presence of the tumour before operation varies between one month and several years, and up to 20 years' duration is seen (Abel, 1968). In most cases no growth is noticed between its discovery and removal of the tumour. There is also a great variation in age, from 6 months to 61 years. A great number of patients were between 10 and 20 years old. No sex differences were found. Tumours situated in the mediastinum are most often discovered by a routine X-ray examination, and show no symptoms apart from non-specific pressure symptoms. Some patients have general signs like anaemia refractory to iron administration, hypoglobulinaemia, fever, high sedimentation rate, and plasmocytosis. These signs are seen in 50 per cent of patients with the plasma cell type of lesion, while only 3 per cent with the hyaline-vascular or intermediate type have general signs. A striking feature is the complete and rapid disappearance of general signs after surgical extirpation. Even after incomplete removal, complete remission is the rule. Recurrence of the tumour is never seen, but in one case of incomplete removal regrowth in the residual tissue was seen (Abel, 1968).

In some cases radiation therapy was performed because of a primary malignant diagnosis, but no radiation sensitivity was found.

Case history

A 49-year-old unskilled labourer was referred to our ambulatory under the diagnosis of 'tumour of the left submandibular gland'. Nine months earlier, he had discovered a painless tumour under the left mandibular angle. Since then, he had noticed a slight growth and tenderness of the tumour, but no real pain. Objectively we found an indolent tumour in the position of the left submandibular gland, not adherent to the surrounding structures. The estimated size was that of a hen's egg. X-ray examination of the gland was normal. X-ray examination of the jaws disclosed changes in the teeth with partial retention of $\div 8$ and resorption of interdental bone and deep periodontal pocket formation in connection with $\div 6$, $+5$, and $+6$. After extraction of the affected teeth, development of an alveolitis sicca dolorosa of $+6$, with sequestration and perforation to the

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maxillary sinus, took place. The defect was closed operatively. However, the tumour remained unchanged and a needle biopsy from the lesion only revealed normal lymphatic tissue.

It was decided to remove the tumour. At operation, a well demarcated tumour was found in close connection with the submandibular gland, slightly adherent to its surface. No post-operative complications and no signs of recurrence were seen after 8 months.

Patho-anatomy in the present case

The tumour was solitary, round, well-demarcated, and encapsulated. The cut surface appeared greyish, slightly nodular and without any signs of bleeding, necrosis, or cysts. Microscopically, the tumour was of the intermediate type, with evenly distributed nodules in both cortex and medulla. Subcapsular remnants of marginal sinuses but no medullary sinuses were evident. The nodules varied in size and shape and a few were confluent. The follicle centres also varied; some were normal bright reaction centres and others showed typical vascularization and hyalinization. The inter-follicular stroma was made up by proliferating vessels with prominent endothelial cells, large coarse reticulum cells, small mature lymphocytes, plasma cells, and in many places very many eosinophilic granulocytes.

Differential diagnosis

The tumour has the same multinodular structure as some other lesions, both malignant and benign. Especially by freezing microscopy, the diagnosis might be difficult. A nodular lymphoma may be suspected in the presence of nodules throughout the cut surface but the total lack of abnormal cells should correct the diagnosis. The rich vascularity, hyalinization and plasma cell infiltration are not features of malignant lymphoma. In Hodgkin's disease of the mixed-cellularity type, the presence of plasma cells, eosinophilic granulocytes and prominent reticulum cells increases the resemblance to the lesion under discussion, but no Reed-Sternberg cells are found. However, one author claims to have found Reed-Sternberg cells in a case of angiofollicular lymph node hyperplasia, and the cells behaved like tumour cells when cultivated in the hamster cheek pouch (Fischer *et al.*, 1970). Follicular lymph node hyperplasia in rheumatoid arthritis also presents a differential diagnostic problem, but this lesion seldom represents a single tumour, a feature which holds most of the differential diagnostic possibilities. In the rheumatic lesion one also expects to find neutrophils (Nosanchuk and Schnitzer, 1969). The viral lymphadenitis seen with mononucleosis and herpes zoster, and post-vaccinially is also characterized by diffuse follicular hyperplastic vascular changes, and a mixed cellular response, including reticular lymphoblasts. In fact one of the cases of the first extrathoracic type (Cohen, 1957) was from a patient after a recent injection of diphtheria-tetanus toxoid. In subcutaneous angioblastic lymphoid hyperplasia (Reed and Terazakis, 1972), the vessels are larger, with thicker walls, and this tumour lacks a capsule.

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The above-mentioned differential diagnosis also serves as a clinical differential diagnosis as well. Beside these, the primary diagnosis of a brachogeneic cyst has been made (Abel, 1968). In one case, the primary diagnosis was tuberculous adenitis because of a positive Mantoux reaction (Agarwal *et al.*, 1973).

Aetiology

The nature and pathogenesis of the lesion is completely unknown, as indicated by the great numbers of synonyms: Castleman's lymphoma, lymph node hyperplasia resembling thymoma, lymphonodal hamartoma, benign giant lymphoma, giant lymph node hyperplasia, follicular lympho-reticuloma, and others. A convincing theory is that the different types of lesion represent successive steps in the evolution of the tumour, with the plasma cell type as the initial lesion and the hyaline-vascular type as the final outcome (Flendrig, 1969). This theory favours the view that the lesion is a reactive process in a lymph node. The nature of the stimulus is not known. One group of authors has found virus particles in the lesion (Fischer *et al.*, 1970). The lesion has some features in common with the follicular hyperplasia seen in rheumatic arthritis (Nosanchuk and Schnitzer, 1969) or postvaccinial adenitis (Hartsock, 1968). In one case the diagnosis of infectious mononucleosis by the heterophil agglutination test coincided with a mass in the neck which proved to be an angio-follicular lymph node hyperplasia (Keller *et al.*, 1972). But in most cases no internal or external stimulus is known. Some authors (Lattes and Fachter, 1962; Abel, 1968) consider the tumour as an angiomatous lymphoid hamartoma or lymphoid choriotoma. These authors deny the existence of lymph node sinuses in the tumour. But at least remnants of marginal sinuses are found by several authors. In an experience of 183 cases, remnants of sinuses are found in 60 per cent (Keller *et al.*, 1972). One author (Zettergren, 1961) expresses the opinion that the lesion is a benign neoplasm, because he finds it extremely improbable that an inflammatory process would give rise to changes confined to a single lymph node, leaving the other lymph nodes in the area unaffected. He suggests the term follicular lympho-reticuloma. As a possible explanation of this monofocal representation, Flendrig (1969) suggests a localized stimulus within the lesion. The nature and origin of this stimulus remain purely speculative.

Discussion

Of about 220 cases we have found in the literature, 29 were situated on the neck. In 22 cases the age and sex, and in only 12 cases the sizes of the tumours are known. All the cases are of the hyaline-vascular or intermediate type. No general symptoms are described in these 29 cases, and no differences in age, sex or tumour size are found compared with the whole group.

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In addition to the cases in the neck, a review of the literature revealed two cases of special oto-rhino-laryngologic interest, namely a tumour in the floor of the mouth of a 22-year-old male (Schumann, 1966) and a tumour in the larynx of a 41-year-old male (Climie *et al.*, 1964). The tumour in the larynx was situated in the right sinus of Morgagni, extending up to the aryepiglottic fold, with complete obliteration of the right sinus piriformis. The patient suffered from hoarseness. In both cases the tumours were removed *in toto* with a complete cure. Both cases were of the hyaline-vascular type. The tumour is most often described in close connection with the sternocleidomastoid muscle, in a few cases close to the carotic sheath and in one case adherent to the trachea. In our case, the lesion simulated a tumour in the submandibular gland. Fine-needle puncture did not lead to any conclusive diagnosis. A chronic inflammatory focus was discovered although there was a discrepancy between the tumour size and the degree of infection.

The persistence of the lesion after extraction of the teeth might be explained by the post-operative complications. As already mentioned, the exact nature of the lesion is not known. In our case an inflammatory focus is present and it is tempting to suggest an inflammatory aetiology, but on the other hand no shrinkage of the tumour was produced by revision of this focus. Lesions of each type exhibit histologic and clinical features commonly associated with infections or inflammations, but the heavy infiltration with plasma cells, the abnormal vascularization and hyalinization, their size, and the fact that the tumours most often are solitary, are not features of the usual forms of lymphadenitis. Complete surgical excision is the treatment of choice, both for establishing the diagnosis and for a direct cure of angiofollicular lymph node hyperplasia.

Summary

One case of angiofollicular lymph node hyperplasia simulating a salivary gland tumour is presented. In a review of the literature containing some 220 cases, 29 cases in the neck were found. A survey of these 29 cases is given, and another two cases of special oto-rhino-laryngologic interest are mentioned. Furthermore, a description of the tumour and a brief discussion of aetiology and differential diagnosis are given.

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Department of Pathology,
Department of Oto-rhino-laryngology,
Sundby Hospital,
DK 2300 Copenhagen,
Denmark.

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