TECHNICAL REPORT
21-69
業 績 報 告 書

RETICULUM CELL SARCOMA OF THE THYROID
CASE-REPORT
AND REVIEW OF THE LITERATURE

甲状腺の細網肉腫，症例報告と文献の検討

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ATOMIC BOMB CASUALTY COMMISSION

国立予防衛生研究所－原爆傷害調査委員会

JAPANESE NATIONAL INSTITUTE OF HEALTH OF THE MINISTRY OF HEALTH AND WELFARE

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HIROSHIMA AND NAGASAKI, JAPAN

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INTRODUCTION

Malignant lymphoma of the thyroid (lymphosarcoma or reticulum cell sarcoma) has for many years been a controversial subject, but the literature contains an increasing number of well documented cases. True lymphosarcoma of the thyroid can occur but must be differentiated from the diffuse small cell carcinoma.[1] At times it is difficult to distinguish histologically thyroid sarcoma from diffuse small cell carcinoma as well as the primary lesion from the disseminated systemic lymphoma with involvement of the thyroid. Warren and Meissner[2] stated that "Lymphomatous tumors of the thyroid are usually (perhaps always) a manifestation of disseminated systemic lymphoma."

The decision as to whether the thyroid is involved by a lymphoma primarily or secondarily is often a matter of judgement based on the clinical history, the gross pathology as well as microscopic findings. Ewing[3] did not accept the occurrence of primary lymphosarcoma of the thyroid. Mikal[4] reported 9 cases of primary lymphoma of the thyroid gland and in a review of the literature quotes 165 cases of primary lymphoma. The review contains 44 cases of lymphoma of the thyroid associated with Hashimoto's disease. Walt et al[5] reported 21 cases as primary malignant lymphoma of the thyroid.

He stated that the gross appearance was not characteristic and the tumor shared many features with small cell carcinoma. The authors noted that the early lesions are well circumscribed nodules while the advanced lesions extend through the capsule of the thyroid and invade the strap muscles, the trachea and esophagus thus usually forming a large mass. The advanced lesion was noted in our case. Welch and Hellwig[6] in their report of four cases of malignant lymphoma of the thyroid described a clinical syndrome which others have also noted. The tumor usually occurs in elderly females with symptoms of rapid enlargement of the neck, dysphagia, dyspnea, weakness, loss of weight, and often hoarseness. Cox[7]

緒　言

甲状腺における悪性リンパ腫，すなわち，リンパ肉腫や細網肉腫は，長年，議論の的であったが，文献に報告される例はしだいに多くなっている．甲状腺に真のリンパ肉腫は起こりうるが，瀰漫性の小細胞性癌との鑑別が必要である．[1] 甲状腺の肉腫と瀰漫性小細胞性癌の区別，または，原発性病変と播種性全身性リンパ腫の甲状腺侵襲との区別が困難な場合がある．Warren および Meissner [2] は，「甲状腺のリンパ腫様腫瘍は一般に（あるいは常に）播種性全身性リンパ腫の発症の一つである」と述べている．

甲状腺のリンパ腫が原発性であるか続発性であるかの判断は，臨床病歴，肉眼的病理所見および鏡検所見に基づいて決定されることが多い．Ewing [3] は，甲状腺の原発性リンパ肉腫の発生を否定している．Mikal [4] は，甲状腺の原発性リンパ腫 9 例を報告し，文献の検討で原発性リンパ腫を 165 例認めている．この中には，橋本氏病に随伴した甲状腺リンパ腫が44例含まれていた．Walt ら [5] は，甲状腺の原発性悪性リンパ腫を21例報告し，その肉眼的所見は特異的ではなく，小細胞性癌と共通の所見が多いと述べた．

かれらは，初期病変は輪郭の鮮明な結節であるが，進行した病変は甲状腺被膜から甲状腺挙筋，気管および食道に侵入して大きな腫瘤を形成することが多いと認めた．われわれの例でも，この進行した病変が認められた．Welch および Hellwig [6] は，甲状腺の悪性リンパ腫 4 例の報告で，他の研究者と同様の臨床的な症候群を記載している．すなわち，この腫瘍は高齢女性に発生することが多く，症状として頚部の急速な腫大，嚥下困難，呼吸困難，脱力感および時には嗄声が認められる．Cox [7] は，

noted that when patients with malignant lymphoma of the thyroid came to autopsy that there was a predilection for metastases to involve the gastrointestinal tract, although widespread metastases may occur. Of the nine cases reported, eight were elderly females and six were of the reticulum cell type. Rafla[8] in a review of 38 cases of anaplastic tumors of the thyroid included 6 cases of reticulum cell sarcoma. No pathological description of the latter is given and their prognosis was no better than the anaplastic tumors. Woolner et al[9] reviewed 46 cases of primary malignant lymphoma of the thyroid, of which 12 were of the reticulum cell type. It was the authors' opinion that it was not justified to classify all small cell malignant lesions of the thyroid as carcinoma.

CASE REPORT

The patient (68AN74) was a 74-year-old Japanese male who first noticed in February 1968 that his stools were black. In April he developed hoarseness, mild dyspnea, and dysphagia. In May he was unable to swallow and had to be fed through a gastrostomy tube. One month later he became markedly jaundiced. His past history was noncontributory.

The physical examination was essentially negative. Blood pressure was 130/0 mmHg. He expired 5 months after the onset of his symptoms.

Laboratory Findings. Urine showed 1 plus protein and urobilinogen was 2+. Total protein level 5.54 g; albumin 2.64 g; globulin 2.90 g. Total bilirubin 16 mg; direct 6.5 mg, indirect 9.5 mg. Cholesterol 161 mg. Serum glutamic oxalacetic transaminase 255; serum glutamic pyruvic transaminase 140; alkaline phosphatase 18.5 B units.

Urea nitrogen 30 mg, creatinine 1.8 mg, serum amyluse 204 units, blood sugar 112 mg. The blood showed a moderate anemia with hemoglobin of 69%, hematocrit 36%. The white blood cell count varied from 7150 to 13,000 with 90% neutrophils.

Autopsy Findings. The body was in a poor state of nutrition. He weighed 29 kg (64 lbs) and was 168 cm (5'6") in length. The conjectivae were slightly icteric. No lymph nodes were palpable. There was a recent tracheotomy wound. In the left hypochondrium there was a gastrostomy wound. The liver extended 7 cm below the right costal margin. No fluid was present and enlarged lymph nodes were not seen. The pleural cavities were obliterated by dense adhesions. The thymus gland was replaced by fat tissue.

甲状腺の悪性リンパ腫例の剖検で広範囲の転移が認められることもあるが，消化器系転移の傾向が特に強いと認めた．かれの報告した9例中8例は高齢女性で，6例は細網細胞型のものであった．Rafla[8]は，甲状腺の退形成性腫瘍38例の再検討に細網肉腫6例を含めた．この6例についての病理所見の記述はないが，予後が退形成性腫瘍より良好であるとは認められなかった．Woolnerら[9]は，甲状腺の原発性悪性リンパ腫46例の再検討を行ない，このうち12例は細網細胞型であり，甲状腺の小細胞性悪性病変をすべて癌とするのは妥当でないと述べている．

症例報告

74歳の日本人男性（68－AN－74）．1968年2月，黒色便に気づいた．4月に嗄声，軽度の呼吸困難および嚥下困難を生じた．5月に嚥下不能に陥り，胃瘻設置による経管的栄養供給が必要になった．1か月後に強度の黄疸が現われた．既往歴に特記事項はなかった．

全身検査はほぼ陰性であった．血圧は130／0 mm Hg．症状の発現から5か月後に死亡した．

臨床検査所見 尿中蛋白＋；ウロビリノゲン＋．血清総蛋白5.54 g；アルブミン2.64 g；グロブリン2.90 g．総ビリルビン16mg；直接型6.5 mg，間接型9.5 mg．コレステロール161 mg．GOT 255；GPT 140，アルカリ性フォスファターゼ18.5 B単位．

尿素窒素30mg，クレアチニン1.8 mg，血清アミラーゼ204単位，血糖112 mg．血液検査で中等度の貧血を認めた：血色素69%，ヘマトクリット値36%．白血球数7150－13,000，好中球90%．

剖検所見 栄養状態不良．体重29kg（64ポンド）．体長168cm（5フィート6インチ）．結膜は軽度に黄染．リンパ節を触れない．最近の気管切開創を認める．左季肋部に胃瘻設置術創がある．肝臓は右肋弓下7 cmに達している．液貯留はなく，リンパ節肥大を認めない．肋膜腔は著明な癒着によって閉塞している．胸腺は脂肪組織で置き代わっている．

The larynx and pharynx appeared normal. The esophagus appeared narrowed at the level of the thyroid cartilage.

The thyroid gland was about one and a half times the normal size. It was firm and could not be separated from the trachea (Figure 1). On sectioning, the entire gland, except for the left upper pole, was replaced by a dense yellowish white firm tumor tissue. The tumor extended through the capsule of the thyroid and into the surrounding structures. Several cervical lymph nodes of up to 1 cm in diameter were present and on sectioning had the same appearance as the tumor in the thyroid gland. Several similar lymph nodes were present at the bifurcation of the trachea.

The liver weighed 900 g. On the surface were three scattered white nodules up to 3 cm in diameter. The sectioned surface was uniform reddish-brown indicating marked congestion. The markings were distinct. In the porta hepatis several small firm lymph nodes up to 1 cm were present.

The spleen weighed 70 g. It was soft and on sectioning was dark purple, red, and moist. No tumor nodules were present.

The left lung weighed 220 g and the right weighed 280 g. The surfaces were covered by thick fibrous tags and on sectioning appeared dry and crepitant. Several hilar lymph nodes up to 1 cm in diameter were present.

The heart weighed 200 g. The myocardium was dark brown. The coronary arteries and the aorta were unremarkable.

The kidneys were of similar size and each weighed 150 g. On sectioning the markings were distinct and several white nodules up to 0.5 cm in diameter were seen in both kidneys.

The adrenals were of normal size and appearance.

The gastrointestinal tract appeared normal and no evidences of bleeding was apparent.

The pancreas weighed 90 g. The head felt firm and on sectioning was white with indistinct lobulations. The body and tail appeared normal. Several firm peripancreatic lymph nodes up to 1 cm in diameter were present. The remaining organs were unremarkable.

Microscopic Examination Multiple sections from both lobes and isthmus of the thyroid showed a diffuse infiltration of small cells of the reticulum cell type in nests

喉頭部と咽頭部は正常．食道は甲状軟骨の高さで狭窄化が認められる．

甲状腺の大きさは正常の約1倍半で硬く，気管より剝離できない（図1）．割面では，左上極部を除く甲状腺全体が稠密な硬い黄白色腫瘍組織で占められている．この腫瘍は甲状腺被膜から周囲構造に侵入している．直径1cmに及ぶ頚部リンパ節を数個認め，その割面は甲状腺の腫瘍と同じ様相を呈した．気管分岐部にも同様のリンパ節数個を認める．

肝臓は重量900 g．表面に最大径3cmの白色結節3個が散在している．割面は一様に赤褐色を呈し，強度のうっ血がある．紋理は明瞭である．肝門部に直径1cmに及ぶ硬固な小さいリンパ節を数個認める．

脾臓は重量70 g．硬度は軟．割面は濃い赤紫色であり，湿潤．腫瘍結節はない．

左肺は220 g．右肺は280 g．表面は厚い線維性付着物でおおわれている．割面は乾燥し，捻髪音を呈す．直径1cmに及ぶ肺門部リンパ節を数個認める．

心臓は重量200 g．心筋は暗褐色である．冠状動脈と大動脈に特記所見はない．

腎臓は左右ほぼ同じ大きさで，重量はそれぞれ150 g．割面では，紋理が明瞭であり，直径0.5cmに及ぶ白色結節を両腎に認める．

副腎は大きさ，外観ともに正常．

胃腸管は正常のようにみえ，出血の形跡はない．

膵臓は90 g．膵頭部は硬固であり，割面は白色を呈し，分葉構造は不明瞭である．膵体部と尾部は正常である．膵臓周囲に直径1cmに及ぶ硬いリンパ節数個を認める．その他の臓器に特記すべき所見はない．

鏡検所見　両葉と峡部より多数の切片を検査した結果，細網細胞型の小細胞による巣状および層状の瀰漫性侵潤

and sheets (Figure 2). The cells contained oval to round nuclei and a scanty eosinophilic cytoplasm. Mitotic figures were scanty and there was a sprinkling of lymphocytes throughout. Occasionally the cells were separated by bands of collagen. There was no attempt of the tumor cells to form definite epithelial structures as is seen in diffuse small cell carcinoma of the thyroid. Colloid follicles were only seen in the left upper pole of the gland. Reticulum stain showed an abundance of reticulum fibers. The tumor extended through the capsule of the thyroid into the trachea and surrounding strap muscles (Figure 3). The lymph nodes were replaced by tumor similar to that seen in the thyroid (Figure 4).

In the liver there were frequent nests of tumor cells of the reticulum cell type (Figure 5). Heavy infiltrations in the portal septa were conspicuous. In addition there was severe pericholangitis with abscess formation. The liver cells contained much bile and iron pigment. The bile capillaries often contained bile casts and bile ducts frequently were the site of abscesses.

The bone marrow was hyperplastic but no tumor cells were present. The spleen was congested and free of tumor.

The extrahepatic bile ducts, the gallbladder and pancreatic ducts showed no changes. The pancreas contained sheets of tumor cells especially in the head. Nests of tumor cells were also seen in both adrenals, kidneys, lungs, pleura, and periadrenal fat tissue (Figure 6).

DISCUSSION

The clinical course of this case was of short duration and the symptoms of dysphagia and hoarseness in the absence of an enlargement in the neck suggested a primary tumor of the esophagus or larynx. The replacement of the thyroid gland by tumor which also involved the surrounding structures and the gross minimal involvement of other organs suggested a primary neoplasm in the thyroid gland. The histological picture of the thyroid showed the tumor to be composed of small cells and in view of the absence of definite epithelial structures, the cells were identified as reticulum cells. Sections from the involved organs showed nests of reticulum-like cells similar to that seen in the thyroid. Again no epithelial structures were recognized. The manner of infiltration of the capsule of the thyroid and its surrounding structures may also be present in small cell carcinoma. The stroma contained focal areas of hyalinization which may or may not be related to a previous thyroiditis. There was no relationship

を認めた（図２）．細胞は卵円形ないし円形の核を持ち，少量の好酸性原形質を含む．分裂像は少なく，全体にリンパ球が散在している．細胞がコラゲン帯によって分離されていることがある．腫瘍細胞は，甲状腺の瀰漫性小細胞性癌のように明確な上皮構造を形成する傾向はない．甲状腺の左上極部のみにコロイド濾胞を認める．細網染色で多量の細網線維を認める．腫瘍は，甲状腺被膜より気管および周囲の甲状腺挙筋に侵入している（図３）．リンパ節は，甲状腺にみられたと同様の腫瘍で占められている（図４）．

肝臓には，細網細胞型の腫瘍細胞巣が多数認められる（図５）．肝門中隔の強度の侵潤が目だつ．そのほか，膿瘍形成を伴う強度の胆管周囲炎がある．肝細胞は，多量の胆汁と鉄色素を含んでいる．細胆管内に胆汁円柱が含まれていることが多く，胆管には膿瘍がしばしば認められる．

骨髄は過形成を呈したが，腫瘍細胞はない．脾臓はうっ血しているが，腫瘍は認められない．

肝外胆管，胆嚢および膵管に変化はない．膵臓，特に膵頭部に腫瘍細胞が層状に存在している．両側副腎，腎臓，肺，肋膜および副腎周囲脂肪組織にも腫瘍細胞巣を認める（図６）．

考　察

本症例の臨床経過が短期間であり，頚部腫脹がないにもかかわらず，嚥下困難および嗄声の症状があったことは，食道または喉頭部の原発性腫瘍を示唆した．また，甲状腺全体が腫瘍で占められ，周囲構造への侵入もあるが，肉眼的には他臓器の侵襲がごく軽度であったので，甲状腺の原発性腫瘍と考えられた．甲状腺の組織像では，腫瘍は小細胞から成っており，明確な上皮構造がみられなかったので，この細胞は細網細胞であると考えられた．侵襲の及んでいる臓器の組織切片を検査すると，甲状腺と同様の細網様細胞巣を認めたが，上皮構造はなかった．甲状腺被膜と周囲構造のこのような侵潤は，小細胞性癌に認められる場合もある．基質内に巣状の硝子化があったが，以前の甲状腺炎と関係があるか否かは不明である．

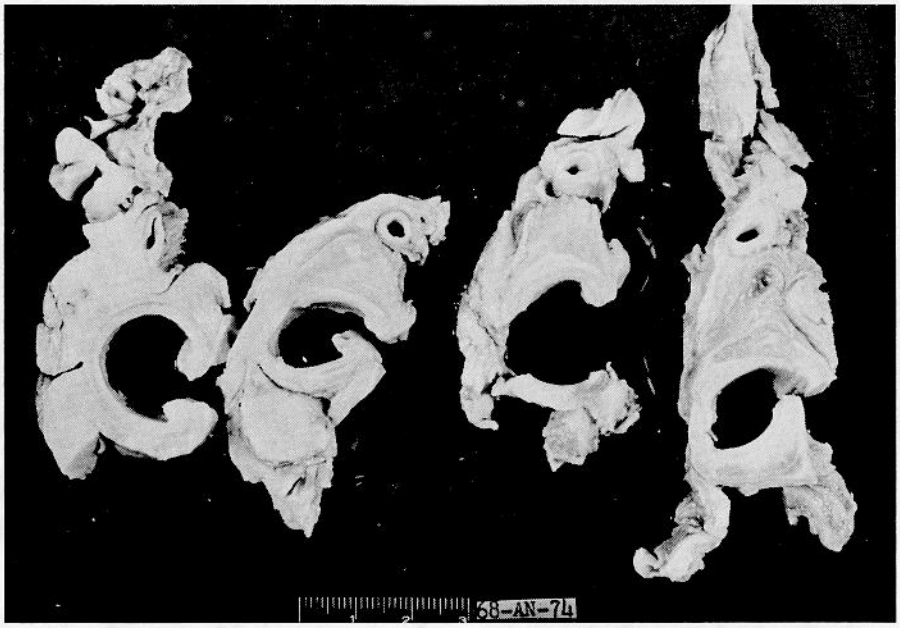


Figure 1 Tumor replacing the thyroid and invasion of the surrounding structures, trachea, and strap muscles.

図1　甲状腺は腫瘍で占められており，周囲構造，気管および甲状腺挙筋の侵襲がある．

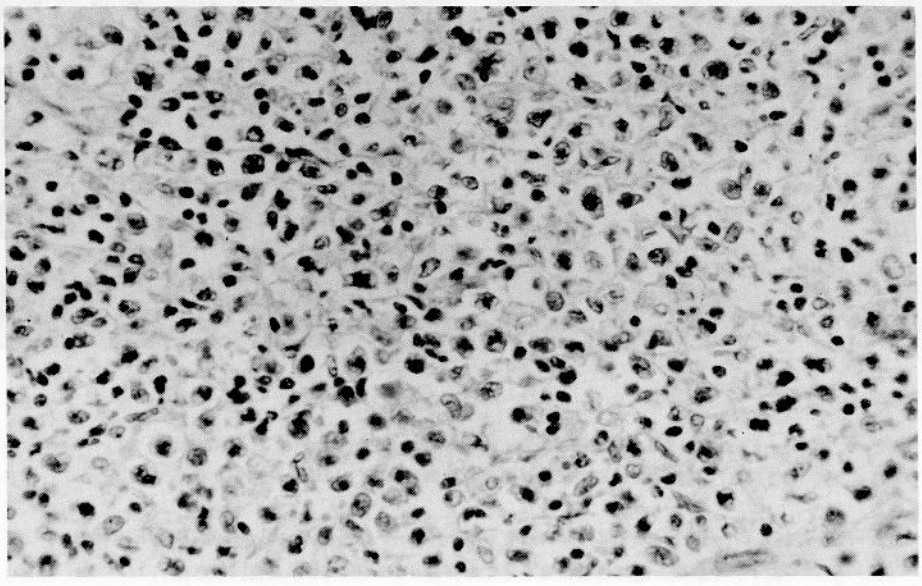
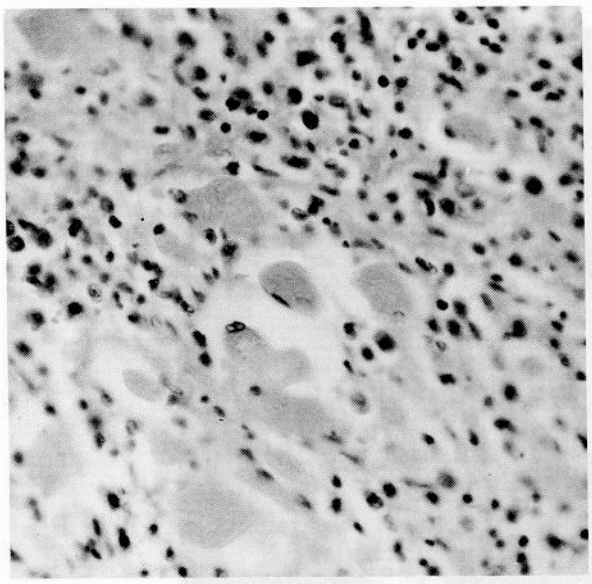


Figure 2 Diffuse infiltration of small tumor cells replacing thyroid gland (H & E ×400).

図2　甲状腺は，小型の腫瘍細胞による瀰漫性浸潤像で占められている（H&E 染色，400 倍）．



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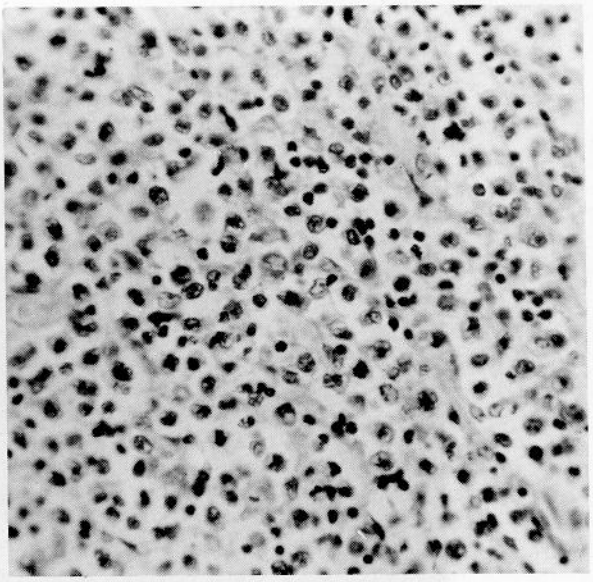

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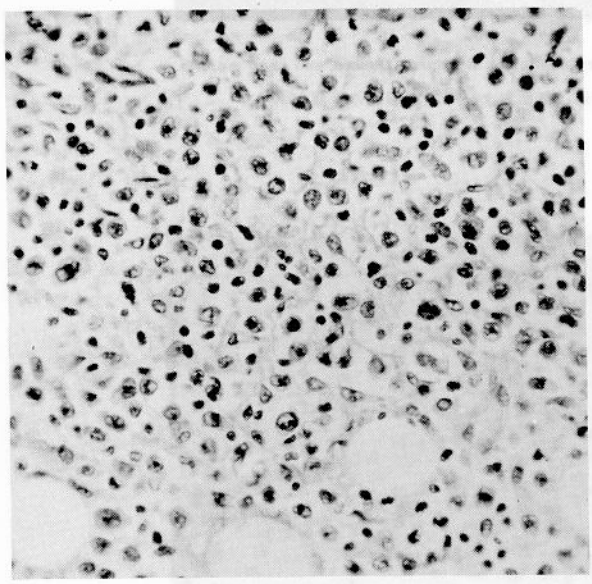

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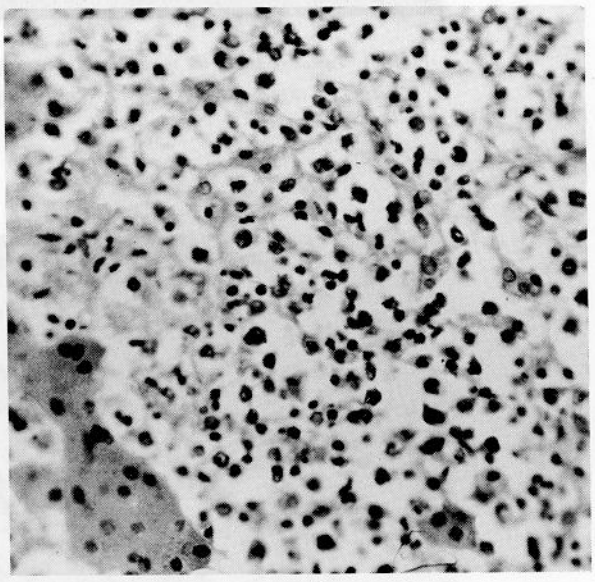

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Figure 3 Tumor cells invading strap muscle in the neck (H & E ×400).

図3　頚部における甲状腺挙筋の腫瘍細胞侵襲（H&E 染色，400 倍）.

Figure 4 A cervical lymph node showing a similar pattern as seen in the thyroid (H & E ×400).

図4　甲状腺と同様の組織像を呈した頚部リンパ節（H&E 染色，400 倍）.

Figure 5 Metastasis to the liver. The character and arrangement of cells are similar to the thyroid(H&E ×400).

図5　肝臓への転移．細胞の性状と配列は甲状腺と同様である（H&E 染色，400 倍）.

Figure 6 Metastasis to the periadrenal fat tissue (H & E ×400).

図6　副腎周囲脂肪組織への転移（H&E 染色，400 倍）.

to Hashimoto's disease which some authors have described in cases of lymphosarcoma. Since our case demonstrated an advanced stage of lymphoma of the thyroid it becomes difficult to state whether the tumor of the thyroid was primary or part of the disseminated process. The histological evidence of minimal involvement of lymph nodes, liver, kidneys, and adrenals would suggest a primary site of the sarcoma in the thyroid. A review of this case was interpreted as a malignant lymphoma, reticulum cell type of the thyroid with systemic involvement.[10] In a review at ABCC of 536 cases of carcinoma of the thyroid gland no cases of primary lymphosarcoma were encountered.[11] Other criteria which are helpful in diagnosing lymphosarcoma of the thyroid are absence of blood vessel invasion, exclusion of tumorous epithelial structures, the monotonous small cell pattern, the study of sections taken beyond the thyroid capsule, and the presence of atrophic residual follicles in the gland.

In a review of 152 autopsy cases of malignant lymphoma from the ABCC files in Hiroshima and Nagasaki there were 71 cases of reticulum cell sarcoma, 44 cases of lymphosarcoma, and 37 cases of Hodgkins disease. The thyroid was the site of invasion in 20 cases (13.1%)—reticulum cell sarcoma 9 cases (5.9%), lymphosarcoma 9 cases (5.9%), and Hodgkins disease 2 cases (1.3%). In all the cases where the thyroid was involved the gross appearance of the gland was well preserved. The histological picture was characterized by interstitial infiltrations of tumor cells, usually focal with preservation of normal follicles. One case contained a small nodule composed of solid tumor cells and surrounded by normal follicles. In a few cases the tumor cells extended into the capsule and stroma of the thyroid from outside the gland. This was in sharp contrast to our case where the gland was practically replaced by solid tumor tissue and a few remaining atrophic follicles noted in the left upper lobe. The evidence supports the probability of primary involvement of the thyroid by the lymphoma.

SUMMARY

A case is reported of a 74-year-old Japanese male ill for 6 months, who, at autopsy, presented a reticulum cell sarcoma of the thyroid and metastasis to the cervical lymph nodes, liver, kidneys, and adrenals. Pericholangitis with abscess formation in the liver was incidently noted. Other lymph nodes in the abdomen were scanty and less than 2 cm in diameter. The monotonous small cell pattern and absence of tumorous epithelial structures in the thyroid and other involved sites support the diagnosis of reticulum cell sarcoma of the thyroid. With the ever increasing

リンパ肉腫と橋本氏病との関係を報告した著者もあるが，われわれの例にはこのような関係は認められなかった．本例では，甲状腺のリンパ腫が進行していたので，甲状線の腫瘍が原発性であるか播種性疾患過程の一部であるか断言できない．ただし，組織学的検査で，リンパ節，肝臓，腎臓および副腎の侵襲がきわめて軽度であると認められたことは，肉腫の原発部位が甲状腺であることを示唆している．本症例の再検討では，全身性侵襲を伴う細網細胞型の甲状腺悪性リンパ腫と解釈された．[10] ABCCにおける甲状腺癌536例の再検討では，原発性リンパ腫は1例も認められていない．[11] そのほかに，甲状腺におけるリンパ肉腫の診断基準としては，血管侵襲の欠如，腫瘍状上皮構造の欠如，単調な小細胞像，甲状腺被膜外の部位から採った組織切片の検査，甲状腺内における萎縮性濾胞の残遺などをあげることができる．

広島・長崎両市のABCCで剖検を行なった悪性リンパ腫152例を再検討した結果，細網肉腫71例，リンパ肉腫44例，ホジキン氏病37例を認めた．甲状腺への侵襲は20例(13.1%)に認められた．すなわち，細網肉腫9例(5.9%)，リンパ肉腫9例(5.9%)およびホジキン氏病2例(1.3%)であった．甲状腺侵襲のあった例では，甲状腺は肉眼的にはよく保たれていた．組織像の特徴は，基質の腫瘍細胞侵潤であり，これは普通巣状を呈し，正常な濾胞が残っている．1例に充実性の腫瘍細胞から成る小結節を1個認め，その周囲に正常濾胞があった．少数例では，腫瘍細胞が甲状腺の外部から被膜と基質内に侵入していた．これに対してわれわれの例では，甲状腺はほとんど完全に充実性腫瘍組織で占められ，萎縮性濾胞が少数左葉上部に残っているにすぎない．この所見は，リンパ腫の原発部位が甲状腺であった可能性を示すものである．

要　約

74歳の日本人男性の1症例．発病から6か月後に剖検の結果，甲状腺の細網肉腫と頚部リンパ節，肝臓，腎臓および副腎への転移が認められた．偶発所見として肝臓に膿瘍形成を伴う胆道周囲炎を認めた．その他の腹部リンパ節は少数で，直径2cm以下であった．甲状腺やその他の侵襲部位に単調な小細胞像がみられることと腫瘍性の上皮構造がないことは，甲状腺の細網肉腫の診断を支持する所見である．文献にこのような例の報告がますます

number of documented cases in the literature, the thyroid must be considered as a possible primary site for lymphosarcoma, chiefly the reticulum cell type.

The final diagnosis of malignant lymphoma of the thyroid must be based not only upon the gross and histologic appearance but also upon the clinical history, the anatomic distribution of the disease, and the response of the tumor to irradiation when treated clinically.

多くなっていることは，リンパ肉腫，特に細網細胞型のものの原発性部位として甲状腺を考慮しなければならないことを示している．

甲状腺のリンパ肉腫の最終的診断は，組織像のみならず臨床歴，疾患の解剖学的分布および放射線照射に対する腫瘍の反応に基づいて決めねばならない．

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