XANTHOMA OF THE BREAST

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In a series of nine hundred (circa) tumors of the breast in which the preoperative diagnosis was carcinoma, histologic examination showed that in three instances the lesion was a xanthoma. Although the diagnostic error in reference to xanthoma was, therefore, small, the rarity of these tumors and their relation to abnormal lipoid metabolism prompts a discussion of them, as well as of the xanthomatous degenerative processes occurring secondarily in inflammations and in true neoplasms in the breast.

Xanthomas are apparently not true neoplasms. A neoplasm has been defined as a more or less circumscribed collection of cells arising wholly independently of the rest of the body, in general growing progressively, and serving no useful purpose in the organism. Xanthomas violate the second premise in the definition, for they have been shown by blood chemistry determinations to be related to an abnormal lipoid metabolism. Before the development of the modern quantitative methods of blood chemistry which enabled this factor to be proved, there were well known clinical findings which suggested it. Xanthomas were known to be most frequent in elderly individuals with diseases of the liver, particularly those complicated by icterus, with nephritis, and with diabetes. Hutchinson, Sangster and Crocker, for instance, found that four-fifths of the 28 cases of xanthoma multiplex which they collected in 1882 were associated with chronic jaundice. Török made a similar report. Chauffard and Laroche in 1911 first made blood cholesterol determinations in cases of xanthoma and found the cholesterol content to be distinctly elevated. This finding has since been verified by many workers. It has even been shown that when the blood cholesterol falls as the result of the administration of a cholesterol-free diet or because of treatment of coexisting diabetes, the xanthomas may disappear. Xanthomas are thus the local manifestation of a syndrome which may be called xanthomatosis.

THE CLASSIFICATION OF XANTHOMAS

The term xanthoma covers such a variety of disease types that it would appear that the understanding of xanthomas of the breast...
would be facilitated by a brief survey and classification of the types of xanthoma in general. A division into two broad groups on the basis of whether the tumor is a primary xanthoma, made up wholly of xanthoma cells, arising as a local manifestation of the syndrome of xanthomatosis, or a secondary degenerative process in an inflammatory or neoplastic lesion, would seem to be the simplest classification. Such a classification closely follows those proposed by Siemens and by Aschoff. The terminology follows:

A. Primary Xanthoma (Simple hematogenous cholesterosis, Siemens; Xanthoma, Aschoff): A tumor composed wholly of xanthoma cells, and arising as a local manifestation of the syndrome of xanthomatosis.

B. Secondary Xanthomatous Degeneration in (1) neoplasms and (2) inflammatory processes (Inflammatory-degenerative cholesterosis, Siemens; Pseudoxanthoma, Aschoff).

A. Primary Xanthoma

Most of the types of xanthoma can be grouped as subvarieties of the syndrome of xanthomatosis. They will have in common a proved etiology of disturbed lipid metabolism. They will have, also, a common histologic structure, the unit in which is the characteristic xanthoma or foam cell. This is a very large cell, measuring usually between 30 and 50 microns in diameter. It is often round but adapts its shape to the interstices in the connective-tissue stroma in which it lies. The nucleus is very small and round. The cytoplasm, which makes up most of the cell, stains lightly. Under high power its foamy appearance is seen to be due to a fine network in which droplets of cholesterin esters are contained. These tumors present no evidence of inflammatory origin in the form of lymphocytic, polymuclear or plasma-cell infiltration. They are not associated with other varieties of neoplasms. They contain occasional giant cells, which usually lie in the vicinity of the crystals of cholesterin esters which are scattered throughout the tumor. These crystals, as well as the intracellular droplets, when studied in unstained sections after fixation in formalin, are doubly refractive to polarized light. The subvarieties of xanthoma included in this primary syndrome of xanthomatosis are as follows:

(1) Xanthoma palpebrarum: This is the most frequent type of xanthoma. It has been recognized and described by dermatologists for over a century. The characteristic plaques and nodules,
citron-yellow to saffron or brown, are symmetrically situated on or about the eyelids. They develop slowly, usually in middle age or old age, and persist throughout life.

(2) Xanthoma multiplex: Under this designation are grouped those less frequent cases with multiple xanthoma nodules situated most frequently on the scalp, knees, elbows, buttocks, or fingers. It is noteworthy that these regions are those most exposed to trauma. The mucous membranes, particularly the cornea and buccal mucosa, may also be involved. The distribution often follows the folds of the skin and is usually symmetrical. Autopsy in these cases may show xanthoma nodules in any of the viscera, but particularly in the liver, spleen, and meninges. In a considerable percentage of cases disease of the liver, such as cirrhosis or some type of toxic or infectious hepatitis, is found. Sikemeier collected a series of cases of this type and reported one in which the liver was the seat of localized tuberculosis.

Most of the recently reported cases of xanthoma multiplex have included blood analyses, which showed an elevated blood choles terin. Richter (Case 1) described a case of this type in which the blood cholesterol on admission was 650 mg. per cent. After the patient had been on a choles terin-free diet for six weeks the blood cholesterol had fallen to 281 mg. per cent and the xanthoma nodules had become softer and smaller. Although the blood cholesterol has generally been found to be elevated, there are reports of isolated cases, such as those described by Siemens and by Rosenbloom, in which it remained within normal limits. Schmidt has emphasized that the hypercholesterinemia may be intermittent, and that repeated determinations are therefore necessary.

Chalipsky and Veger have called attention to a group of cases in which xanthoma multiplex occurs in association with hypogenitalism and disturbed ovarian function. They describe one such case which they observed.

In a small group of cases xanthoma seems to be familial. This type of the disease has the same anatomic distribution as xanthoma multiplex except that the eyelids do not seem to be involved. The lesions may be congenital or may appear at any time before puberty. There is no evidence of associated liver disease. Mac kenzie and Startin described two families in each of which there were several members affected by the disease. Arning and Lippmann observed xanthomatosis in a mother and in five of her nine children. Hufschmitt and Nessmann have recently reported a
family in which three sisters had xanthoma nodules of the hands and feet and hypercholesterinemia. Schmidt has described a family in which all five offspring of a healthy father and mother were affected. At one time or another all the children showed hypercholesterinemia.

(3) Xanthoma diabeticorum: These rare cases may present generalized xanthomas involving the skin, mucous membranes, serous surfaces, liver, spleen, and many other viscera. Lubarsch reported a case in which the xanthomatosis was particularly prominent in the liver, lymph nodes, gums, bone marrow, and appendix. He believes that, in addition to the underlying hypercholesterinemia, a condition of lymphoid stasis is concerned in xanthomatosis. In such lymphoid stasis he sees the explanation for xanthomatosis being most prominent in the organs containing lymphoid tissue, as in his case. At autopsy of a woman dying with diabetes Petri found a massive xanthoma of the mesentery. In an attempt to identify the particular lipoids contained in the tumor, many staining reactions and methods of chemical analysis for different lipoids were employed. The most significant finding was a total cholesterol content ten times that of normal mesenteric tissue.

Major studied three cases of xanthoma diabeticorum which showed an elevated blood cholesterol. Following suitable diabetic treatment the blood cholesterol fell to within normal limits and some of the xanthoma nodules disappeared. Richter, Wile, Eckstein, and Curtis, and also Ralli have described similar cases in which the xanthoma nodules regressed when the patient was put on a diabetic régime. Ralli's case was particularly noteworthy in that the patient had a pituitary tumor and acromegaly associated with true diabetes mellitus.

(4) Christian's-Schüller's Disease: In 1916 Schüller described the cases of two children with defects in the skull and exophthalmos. The elder, a boy aged sixteen, also showed dystrophia adipogenitalis, and the younger, a girl aged four, had diabetes insipidus. In 1919 Christian reported the case of a child aged five with defects in the membranous bones, exophthalmos, and diabetes insipidus. Occasional cases presenting the features of this peculiar syndrome continued to be reported without any light being thrown on the pathogenesis of the disease. Several cases were autopsied, and yellowish or brownish growths eroding the base of the skull and in other viscera were found; they were interpreted as inflammatory or
Weidman and Freeman autopsied a case (Case 2) which in addition to the typical features of the disease showed hypercholesterinemia. They did not recognize, however, that it was a case of Christian’s-Schüller’s disease and regarded the xanthomatous character of the lesions as secondary to chronic inflammation.

In 1928 Rowland described two cases, from the study of which he was able to show that the disease is a form of generalized xanthomatosis dependent upon an underlying hypercholesterinemia. In addition to the triad of symptoms mentioned above, Rowland’s patients showed loose teeth, chronic otorrhea, dwarfism, and dystrophia adiposogenitalis. In the case in which the blood cholesterol was determined it was found to be elevated. The other case came to autopsy. The base of the skull was found to be extensively eroded and the sella turcica destroyed by yellowish tissue made up of typical xanthoma cells. The ilium contained a similar tumor. In addition there was lipoidosis of the interstitial cells of many organs, including the thyroid lymph nodes, kidneys, liver, lungs, heart, and bone marrow. Rowland found reports of sixteen other cases. In two-thirds of these the onset of the disease was during the second year of life.

Chiari has recently reported a typical case of Christian’s-Schüller’s disease in a man aged twenty-nine. This is the oldest patient on record. Chiari’s pathologic study of this case is, moreover, the most complete yet made in this rare disease. He has found reports of 21 other cases.

(5) Solitary Xanthomas: This group includes the solitary, tumor-like xanthomas which may occur in almost any part of the body. They have been called xanthosarcomas by the English and Germans, and xanthomes en tumeurs by the French. Although rare, they apparently constitute a distinct type of primary xanthoma belonging to the syndrome of xanthomatosis. They are entirely made up of xanthoma cells and show no evidence of degeneration nor any leukocytic or plasma-cell infiltration indicative of a chronic inflammatory process. Pick and Pinkus described tumors of the tongue, parotid, and vulva which fall into this class. Hutter reported a very large solitary xanthoma arising from the skin over the sternum which was accompanied by hypercholesterinemia. The writer has observed this type of tumor in the tongue. The xanthoma cells formed tumor-like groups of cells and infiltrated the surrounding muscle, which appeared to be normal.
B. SECONDARY XANTHOMATOUS DEGENERATION

(1) Secondary Xanthomatous Degeneration in True Neoplasms:

Much confusion has arisen in the classification of xanthomas because of the fact that various types of true neoplasms showing xanthomatous degeneration have been improperly designated by some writers as xanthosarcomas or xanthomas, thus failing to distinguish them from primary xanthomas occurring in the syndrome of xanthomatosis, which have been discussed above. The fundamental distinction between the two groups is made upon their histologic structure. Primary xanthomas are made up entirely of xanthoma cells. On the other hand, the true neoplasms showing xanthomatous degeneration, as their name would indicate, contain not only xanthoma cells but also the epithelial or other type of cell characterizing the neoplasm. As Borst has emphasized, these tumors should not be called xanthomas, but should be designated as xanthomatous carcinomas, etc., according to the true nature of the particular neoplasm in question.

Such xanthomatous degeneration is seen in a wide variety of neoplasms. It occurs in neurofibromas, and it is not uncommon in neurogenic sarcomas. Epithelial tumors of different types show it. Dubs, for instance, described two cases of xanthomatous adenocarcinoma of the fundus of the uterus. Petri reported a xanthomatous adenocarcinoma of the stomach. Corten described a xanthomatous epithelioma of sebaceous gland origin developing in the thigh. Dietrich reported a retroperitoneal sarcoma which was xanthomatous, and Wessen a similar retropleural tumor. Ovarian cysts very often show xanthomatous degeneration.

Xanthomatous degeneration usually occurs in a poorly nourished, frequently central portion of a tumor. The necrotic tumor cells are replaced by foam cells which, as far as cell morphology is concerned, resemble the xanthoma cells which occur in primary xanthomas. The lipoid which they contain is also usually of the same double-refracting type as that found in primary xanthoma. That this is not always the case, however, was shown by Petri, who found only neutral fat in the tumor which she reported. It is important to note that Mallory considers these xanthoma or foam cells which occur as a secondary degenerative phenomena in true neoplasms, and in granulomas, to be fatty endothelial leukocytes. He regards the double-refracting cholesterol content of these cells, as well as the rhomboid cholesterol crystals sometimes occurring with them, as being the product of fatty degeneration
and necrosis of cells. Whether secondary xanthomatous degeneration in neoplasms is correlated with hypercholesterinemia has not been determined. Blood cholesterol determinations have been done in only a few of these cases. In the two cases of xanthomatous carcinoma reported by Dubs there was no hypercholesterinemia.

Because of their comparative frequency, and because their questionable nature has led to a confusing terminology, the giant-cell tumors showing xanthomatous degeneration which occur in the aponeuroses, tendon sheaths, and joint capsules of the extremities deserve to be considered as a separate group. These tumors have been designated by a great variety of names, including giant-cell sarcoma, xanthoma, xanthosarcoma, myeloxanthoma, myeloma, fibroma, granuloma, and endothelioma. They are the most frequently seen of all the varieties of tumor which contain foam cells. Growing slowly over a period of years, and perfectly benign, they form a distinct type of tumor. They are characterized in the gross by their encapsulation and, depending upon the extent to which xanthomatous degeneration has gone, by their yellow or brown color. Histologically they consist of spindle or polyhedral cells which some authors regard as endothelial, giant cells of the foreign body type, foam cells, lymphocytes, and a connective tissue stroma, which may be very dense. Cholesterin crystals and hemosiderin pigment may be prominent. The structure varies a great deal. Some tumors are cellular and made up entirely of the spindle or polyhedral cells. In others the giant cells predominate. In many the xanthomatous degeneration has progressed to such a degree that the tumor is almost wholly made up of foam cells. Unfortunately these giant-cell tumors showing xanthomatous degeneration have come to be regarded as a separate group and are often improperly designated as xanthomas or xanthosarcomas. In reality they are but a variation of the banal giant-cell tendon sheath tumor.

Weil, Landois and Reid, Broders, and Garrett have reported series of cases of these xanthomatous giant-cell tumors. Kirch was the first to appreciate, however, that they are not true xanthomas but simply neoplasms in which secondary xanthomatous degeneration has occurred. In his opinion any type of cell may be transformed into a foam cell by the deposition of cholesterin. Kirch made blood cholesterin determinations in seven patients with tumors of this type and found an elevated cholesterin in
every instance. He therefore concluded that in secondary xanthomatous degeneration in true neoplasms, just as with primary xanthomas, there is an underlying hypercholesterinemia.

Fleissig, and more recently Seyler, have preferred to classify these giant-cell tumors of tendon sheaths as granulomas.

(2) Secondary Xanthomatous Degeneration in Chronic Inflammatory Processes: In a great variety of chronic inflammatory processes the same type of xanthomatous degeneration occurs as has just been described in neoplasms. The foam cells appear scattered among the lymphocytes, plasma cells, and polymorphonuclears which characterize the lesion. Such xanthomatous degeneration is particularly common in chronic salpingitis, and in the walls of old abscesses. It has been reported in abdominal scars, at the site of arsenic injections, in pock-marks, in the scars of herpes zoster, and at the sites of previous chronic skin affections of various types. There are no available reports of blood cholesterin determinations in lesions of this type.

XANTHOMA OF THE BREAST

Tumors of the breast containing xanthoma cells may be discussed on the basis of the classification outlined above for xanthomas in general.

A. Primary Xanthoma of the Breast

The localization of solitary xanthoma in the breast as part of the syndrome of xanthomatosis must be exceedingly rare. A search of the medical literature reveals only one case report of the condition. Cheatle described a circumscribed but not encapsulated xanthoma which he removed from the breast of a woman aged thirty-eight. Blood cholesterin determinations were not done.

The following three cases are examples of this type of tumor observed at the Memorial Hospital in a series of 900 (circa) tumors of the breast in which the preoperative diagnosis was carcinoma. In one of these cases the breast was removed, and only when the histologic sections were studied did the diagnosis of xanthoma become apparent. In the two other cases a local excision of the tumor was done and a diagnosis of xanthoma made from the yellow color of the gross specimen.

Case 1: C. B. T., an unmarried Irish woman, aged seventy-four, was referred to Dr. James Duffy at the Memorial Hospital for treatment on Aug. 17, 1930.
Past History: There was no history of cancer in her family to her knowledge. She had never been ill except for a fractured knee many years ago. She had lost 21 pounds within recent years, having formerly weighed 170, now 149.

Present Illness: Five years previously, about 1925, she had first observed a small lump in the upper inner portion of the left breast. It had grown very slowly to attain its present bulk. It had been painless. The patient had no cough or bone pains.

Physical Examination: The patient was a fairly well nourished, elderly woman. Most of her fat was abdominal. Scattered over her skin, most prominent on the abdomen and face, were many brown to black macular and papular lesions which resembled senile keratoses. The heart and lungs were not remarkable. The blood pressure was 165 systolic and 70 diastolic.

Occupying the upper inner quadrant of the right breast was a tumor (Fig. 1) measuring 9 cm. in diameter and elevated 4 cm. above the surface of the breast. The skin over it was reddened and shiny. The middle of the tumor was soft—suggesting a central area of necrosis. It was slightly movable over deeper structures. The nipple was not retracted. There were no nodes palpable in the right axilla or supraclavicular space. In the left axilla several small, soft nodes were felt.

Repeated urine examination frequently showed a trace of albumin and occasional granular casts. Blood urea nitrogen was 12.1 mg. In addition the urine regularly contained sugar—as much as 2 per cent. Blood sugar on admission was 166 mg. Roentgenograms of the chest were negative.

A diagnosis of adenocarcinoma of the breast with impending ulceration, and chronic nephritis and diabetes was made.
FIGS. 3 AND 4. CASE 1: PRIMARY XANTHOMA OF THE BREAST. × 100 AND × 300
Fig. 5. Case 1: Xanthoma Cells Containing Cholesterol Ester Droplets Sudan III, Counterstained with Hematoxylin
Treatment: The patient was seen in consultation by Sir Lenthal Cheatle, who advised interstitial radiation. Accordingly, on Aug. 26, 1930, and during the following days, six needles containing a total of 85 millicuries of radon filtered by 0.3 mm. of gold and 0.2 mm. of steel were inserted into 18 sites about the periphery of the tumor and allowed to remain in situ until a total of 7,200 milicurie hours had been delivered to the tumor.

Ten weeks later, Nov. 5, 1930, there was a marked decrease in the size of the tumor. A reaction, limited to reddening and slight desquamation of the overlying skin, had occurred. The central area of softening was less marked.

By March 12, 1931, seven months after the radiation had been completed, the contour of the breast was almost normal (Fig. 2). The reddish discoloration of the skin had completely disappeared, only slight post-radiation pigmentation remaining. Of the tumor, only an indefinite area somewhat more firm than normal mammary tissue remained. Because it was felt that, although there had been remarkable regression, a residuum of the tumor persisted, a local mastectomy was decided upon. The diabetes had responded readily to a dietary régime and was not considered a contraindication. On June 4, 1931, the operation was done, novocaine infiltration anesthesia being used. Recovery was uneventful.

On discharge the patient was cautioned to continue her dietary régime. A year later (June 10, 1932) there had been no recurrence of the tumor. At that time her blood sugar was 143 mg. The blood cholesterin was 175 mg., that is within the upper limits of normal. It may, of course, be objected that had a blood cholesterin determination been made at the time the tumor was treated, a year previously, and before the institution of a restricted diet, hypercholesterinemia might have been found. Kirch, however, in his series of xanthomatous tumors, found hypercholesterinemia persisting as late as ten years after operation.

Gross Diagnosis (Pathologic Specimen No. C 4119): A simple mastectomy has been done. Four centimeters from the nipple there is an encapsulated, centrally necrotic tumor measuring 6 x 4 x 6 cm. Its cut surface is soft, reddish, and granular, suggesting bulky adenocarcinoma.

Microscopic Diagnosis: The tumor is composed wholly of very large xanthoma cells lying in the interstices of a prominent fibrous stroma (Figs. 3 and 4). The xanthoma cells are round when they lie free and polyhedral when they lie among the strands of fibrous stroma. They vary between 30 and 50 microns in diameter. The nuclei are comparatively very small, stain darkly, and are often eccentrically situated. The cytoplasm, which makes up the great bulk of the cell, is acidophile and has the characteristic foamy appearance. With higher magnification this is seen to be due to the presence of a fine network in the cytoplasm. Stained with Sudan III (Fig. 5) this network is seen to contain orange-red cholesterin ester droplets. A few crystals (Fig. 6) surrounded by giant cells of the foreign-body type are seen. Large areas of the tumor are necrotic. The tumor contains no lymphocytic, plasma-cell, or polymorphonuclear infiltration. No neoplastic elements are seen. The vascular supply is poor.
Studied with the polarizing microscope, formalin fixed and unstained sections show the intercellular droplets and the crystals to be doubly refracting.

*Diagnosis:* Primary xanthoma of the breast.

**Fig. 6. Case 1: Cholesterol Ester Crystals Surrounded by Foreign-body Giant Cells in Xanthoma of Breast**

**Case 2:** A. M., a married American woman, aged forty-one, came to the Memorial Hospital on Dr. Douglas Quick's service, April 1, 1928.

*Past History:* The patient had never been pregnant. She had occasionally had slight pain in her breasts with menstruation.

*Present Illness:* The lump in the left breast was first noticed one month previously. The patient could not recall any trauma to the breast.

*Physical Examination:* The patient was a poorly nourished woman. In the inner lower quadrant of the left breast was a discrete, firm, freely movable tumor about 1 cm. in diameter. There was no skin adherence, or nipple retraction. In both axillae were enlarged but soft nodes. Roentgenograms of the chest were negative. The urine contained a trace of albumin, and many hyaline casts were seen. Its specific gravity was 1.030.

*Treatment:* A diagnosis of probable chronic mastitis was made, but to exclude carcinoma it was decided to excise the tumor. Preoperative roentgen radiation was given over the tumor in April, and during the
FIGS. 7 AND 8. CASE 2: PRIMARY XANTHOMA OF BREAST. × 100 AND × 400
following month it diminished distinctly in size. In May 1928 excision was done. Three years later there had been no recurrence.

*Gross Diagnosis* (Pathologic Specimen No. B 4810): The specimen consists of a wedge of breast tissue in which there is a well circumscribed yellowish nodule 0.5 cm. in diameter. Gross diagnosis: Xanthoma.

*Microscopic Diagnosis:* The tumor is made up of xanthoma cells lying in a fibrous stroma (Figs. 7 and 8). The cells are between 20 and 40 microns in diameter. The nuclei are relatively small. The foamy cytoplasm stains very lightly. Scattered foci of lymphocytes are seen.

*Diagnosis:* Primary xanthoma of the breast.

**CASE 3:** M. H. L., an Irish widow, aged thirty-eight, came to the Memorial Hospital, Nov. 10, 1926.

*Past History:* One sister had had a tumor of the breast. The patient had had three normal pregnancies and had nursed all three children. The last lactation was in 1921.

*Present Illness:* In March 1925, the patient had noticed a lump in her left breast, and in August 1926 a radical mastectomy was done in a New York hospital. In November 1926 she came to Memorial Hospital complaining of dyspnea.

*Physical Examination:* Examination showed a group of hard nodes in the left supraclavicular region. Roentgenograms of the chest were negative. The scar showed no evidence of recurrence.

*Treatment:* A diagnosis of carcinoma metastasis was made and treatment with the radium element pack was given over the supraclavicular nodes.

In January 1927 a freely movable, hard subcutaneous nodule about 1 cm. in diameter was observed near the edge of the scar, in the anterior axillary line over the 9th costal cartilage. This was thought to be a recurrence of carcinoma and was excised under novocaine anesthesia. At this time the patient was fairly well nourished, although she was anemic. Several urine examinations were negative for sugar and albumin.

In March 1927 the patient began to have pain in the back. Roentgenograms taken in April showed widespread metastases in the lumbar spine, pelvic bones, and upper femora. Death occurred in October 1927.

*Gross Diagnosis* (Pathologic Specimen No. B 1497): On section of the nodule excised from the chest wall a small, yellowish, solid, opaque nodule 2 mm. in diameter is seen. It is not adherent to the skin but rests on the fascia and is freely movable. Gross diagnosis: Xanthoma.

*Microscopic Diagnosis:* The tumor is a small nodule, surrounded by fat, and composed wholly of xanthoma cells lying in a fibrous stroma (Figs. 9 and 10). The cells average 40 microns in diameter and are irregularly polyhedral in shape. The nuclei are comparatively small, and stain darkly. The cytoplasm is amphophilic and contains a fine fibrillar network. There is no lymphocytic infiltration. Carcinoma cells are not seen.

*Diagnosis:* Primary xanthoma of chest wall at site of amputated breast.
Figs. 9 and 10. Case 3: Primary Xanthoma of Chest Wall at Site of Amputated Breast. × 100 and × 400
COMMENT: These three cases of xanthoma are presumably examples of the solitary tumor-like type of primary xanthoma occurring in the syndrome of xanthomatosis. In the first patient the presence of diabetes as well as nephritis suggests a disturbed cholesterin metabolism. The blood cholesterin was found to be within normal limits when it was determined a year after operation. The second patient had nephritis, a frequent cause of xanthoma. In the third patient there was no apparent correlation between the supraclavicular and bone carcinoma metastases and the finding of a pure xanthoma in the subcutaneous tissue of the chest wall at the site of the amputated breast.

B. Secondary Xanthomatous Degeneration in the Breast

(1) Secondary Xanthomatous Degeneration in True Neoplasms of the Breast: Groups of foam cells are not infrequently seen in fibroadenomas and carcinomas of the breast. They occur as a degenerative phenomenon in the poorly nourished or necrotic portions of these tumors. The fact that the breast is a fatty organ, and in addition secretes fat-containing milk which may be inspissated, may favor such xanthomatous degeneration in neoplasms of the breast. In any event it is a common finding. Lobeck has made the most complete study of the subject. In 118 amputated breasts he found secondary xanthomatous degeneration sixteen times in carcinoma and once in a fibro-adenoma. He did blood cholesterin determinations in thirteen of these patients and found what he considered an abnormally high blood cholesterin in every instance. Gross described a large fibro-adenoma of the breast showing secondary xanthomatous degeneration. The patient's blood cholesterin was markedly elevated (400 mg.). Hedinger and Miller have also reported xanthomatous fibro-adenomas.

No attempt will be made to report all the instances of breast neoplasms showing secondary xanthomatous degeneration in the records of the Memorial Hospital. The condition is too inconsequential to warrant such attention. The following is an illustrative case of secondary xanthomatous degeneration occurring in a giant intracanalicular fibro-adenoma.

CASE 4: D. K., a married American woman, aged fifty-six, came to the Memorial Hospital, Dec. 23, 1928.

Past History: She had had seven normal pregnancies and had nursed all seven children for more than two years without any difficulty with her breasts. The last lactation had been twenty-six years before.
Figs. 11 and 12. Case 4: Fibro-adenoma of breast showing secondary xanthomatous degeneration. × 100 and × 400
Present Illness: Thirty-seven years previously, while she was nursing her first baby, the patient had noticed a lump within the right nipple. About one year before admission she noticed that the whole right breast was enlarged. For one month there had been intermittent bleeding from the right nipple.

Physical Examination: The whole right breast was occupied by a huge multilocular, cystic tumor which was not adherent to the overlying skin. The tumor was movable over the chest wall. There were no palpable axillary or supraclavicular nodes. The urine showed 0.8 per cent sugar and a trace of albumin but no casts. The blood sugar was 145.6 mg. The blood pressure was 150 systolic and 74 diastolic.

A presumptive diagnosis of papillary cystadenocarcinoma was made.

Treatment: The patient was put on a diabetic régime until her diabetes was in a satisfactory condition and on May 11, 1928, a local mastectomy was done. Healing was without incident and the patient continues free of disease three and one half years later.

Gross Diagnosis (Pathologic Specimen No. B 4717): The specimen consists of a breast bearing an ulceration 6.5 cm. in diameter. The floor of the ulcer is composed of soft lobulated tumor nodules covered with a grayish exudate. On section the breast is seen to be replaced by a tumor mass measuring 15 x 11 x 10 cm. It is enclosed in a thick, fibrous capsule. The tumor is distinctly lobulated throughout, and in its viable portions is composed of firm, gray gelatinous tissue. There are caseous and also calcified areas, as well as degenerated areas containing thick greenish fluid.

Microscopic Diagnosis: The tumor (Figs. 11 and 12) is a giant intracanalicular fibro-adenoma. It is largely myxomatous. Superficially it is infected. In several regions there is well marked xanthomatous degeneration. Here typical foam cells with small round nuclei and a prominent, lightly staining reticular cytoplasm replace the fibrous structure. Numerous crystals surrounded by giant cells are seen.

Diagnosis: Intracanalicular fibro-adenoma showing myxomatous and xanthomatous degeneration.

Comment: In this case the diabetes with its accompanying disturbance in the cholesterol metabolism may have been an etiological factor in the development of secondary xanthomatous degeneration in the breast tumor.

(2) Secondary Xanthomatous Degeneration in Inflammatory Processes in the Breast: Chronic breast abscesses are particularly apt to show secondary xanthomatous degeneration. It has been frequently observed in various types of low-grade inflammation in the breast. Lobeck reported a case of acute mastitis and one of chronic cystic mastitis which contained areas of xanthomatous degeneration and showed an accompanying hypercholesterinemia.

The following case, illustrative of secondary xanthomatous
FIGS. 13 AND 14. CASE 5: CHRONIC BREAST ABSCESS SHOWING SECONDARY XANTHOMATOUS DEGENERATION. × 100 AND × 400
degeneration in an inflammatory process in the breast, is chosen from many instances of this type of lesion in the records of the Memorial Hospital.

**Case 5: L. G., a single white woman, aged 32, was admitted to the Memorial Hospital on Dec. 19, 1929.**

**Past History:** The patient had never been pregnant.

**Present Illness:** Two months previously she had noticed slight tenderness of the right breast. A week later definite redness and elevation of the skin were observed over the tender area. The patient had no temperature but began to feel weak. The breast became distinctly painful.

**Physical Examination:** In the upper outer quadrant of the right breast there was a firm, somewhat cystic, indurated mass measuring 5 x 5 cm. The overlying skin was reddened but not adherent to the mass. There was no skin or nipple retraction. The tumor was tender. In the right axilla there were a few enlarged lymph nodes. Examination of the urine was negative.

**Treatment:** A diagnosis of carcinoma was made, and on Dec. 20, 1929, a radical mastectomy was done by Dr. Frank Adair.

**Gross Diagnosis** (Pathologic Specimen No. B 9365): The breast on section shows a central, softened, necrotic area measuring 3 x 5 cm., which is filled with blood and fibrin. The area is circumscribed by a wall of thickened fibrous tissue.

**Microscopic Diagnosis:** The structure is that of an old breast abscess (Figs. 13 and 14). Plasma cells and lymphocytes predominate. Many polymorphonuclear leukocytes are seen. Scattered throughout are areas where large foam cells, with their characteristic small, dark nuclei and foamy cytoplasm, predominate.

**Diagnosis:** Chronic breast abscess with secondary xanthomatous degeneration.

(3) **Secondary Xanthomatous Degeneration in Traumatic Fat Necrosis in the Breast:** Trauma to the breast may, in unusual cases, produce a localized area of necrosis in the fat which makes up so prominent a part of the organ. In the early stage of necrosis such a lesion consists of a small cavity filled with fatty debris. In the later stage of repair the microscopic picture is quite different, suggesting a granulomatous process in fat. The destroyed fat globules have been replaced by fibrous tissue containing occasional lymphocytes and numerous multinucleated giant cells. Foam cells are a prominent feature. In some areas they surround the fat globules in such a way as to suggest alveoli. They have the characteristic structure of foam or xanthoma cells—a small, dark nucleus lying in a proportionately large, foamy cytoplasm. The appearance of these cells during the repair stage of fat necrosis
FIGS. 15 AND 16. CASE 6: TRAUMATIC FAT NECROSIS OF BREAST, WITH SECONDARY XANTHOMATOUS DEGENERATION. × 100 AND × 200

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lends weight to Mallory's suggestion that they are in reality fatty endothelial leukocytes whose function it is to remove the broken-down fat. The clinical features of traumatic fat necrosis may include fixation to the skin and a degree of induration which makes differentiation from carcinoma impossible. In the gross the tumor often has a yellowish color. Descriptions of this unusual lesion have been published by Lee and Adair, Rowntree, Hadfield, and Keynes.

The following is an illustrative case:

Case 6: S. V., a married white woman, forty-six years of age, was admitted to the Memorial Hospital on April 10, 1930.

**Past History:** She had had two normal pregnancies and lactations, the last twenty-two years previously.

**Present Illness:** There was no definite history of trauma. Two years previously she had noticed a lump in her right breast. It had not increased in size. Occasionally it was painful.

**Physical Examination:** Two centimeters above the right nipple was a firm subcutaneous nodule measuring about 2 cm. in diameter. There was no skin fixation and no palpable nodes were present.

The urine had a specific gravity of 1.005, and contained many hyaline and granular casts but no albumin.

**Treatment:** A diagnosis of fibro-adenoma was made. The tumor was removed locally on April 10, 1930. The patient remained well a year and a half later.

**Gross Diagnosis** *(Pathologic Specimen No. B 10573):* The tumor was a small firm nodule consisting of fat, with small yellow dots scattered through it.

**Microscopic Diagnosis:** Frozen section made possible the diagnosis of traumatic fat necrosis (Figs. 15 and 16). The structure was that of the repair stage of the process. Lying among globules of fat were areas of granulation tissue containing occasional multinucleated giant cells and a great many foam cells. The foam cells tended to arrange themselves in pseudo-alveoli about the fat globules.

**Diagnosis:** Traumatic fat necrosis with secondary xanthomatous degeneration.

**Discussion**

The distinction between primary xanthoma of the breast and secondary xanthomatous degeneration in other disease entities of the breast, which has been made throughout this paper, may seem forced to the reader. It is true that the morphology of the foam cells in the different lesions is identical. A consideration of the structure of each lesion as a whole, however, reveals striking differences, which would appear to warrant the classification which has been adopted. The *primary xanthomas* which have been de-
scribed were made up wholly of xanthoma cells, and contained no neoplastic or inflammatory elements. In the lesions which showed secondary xanthomatous degeneration the general structural features were those of fibro-adenoma, breast abscess, and traumatic fat necrosis, respectively. The foam cells were a secondary phenomenon, apparently concerned with the necrosis of fat.

The presence of a sufficient cause for a disturbance of cholesterin metabolism in two of the three cases of primary xanthoma described (nephritis and diabetes) would suggest that in the breast, as elsewhere, solitary primary xanthoma may arise as a local manifestation of the general syndrome of xanthomatosis. Although very rare, this lesion should be considered in the differential diagnosis of breast tumors, particularly when the patient is diabetic or nephritic, or affected with disease of the liver associated with jaundice. The age of the patient seems to have no particular diagnostic significance—it ranged from thirty-eight to seventy-four years in the present series of cases. The duration of primary xanthoma is likewise apparently not distinctive. It varied between one month and five years in these cases. That primary xanthoma of the breast may grow to be very large and simulate in all respects a bulky adenocarcinoma is shown by Case 1 of the series reported.

There seems to be no way of diagnosing primary xanthoma of the breast preoperatively. Hypercholesterinemia has frequently been found to accompany xanthoma, but apparently the finding is not present constantly in every case, so that numerous cholesterin determinations taken over a considerable interval may be necessary to reveal it. In the one case in this series in which a blood cholesterol determination was made (Case 1) it was found to be within the upper limits of normal.

The reaction of primary xanthoma to radiation is not well enough known to be of any value in differential diagnosis. In the early days of radiation there were conflicting reports as to the sensitivity of xanthoma. Although Evans reported that in a case of xanthoma multiplex treated with roentgen rays the tumor practically disappeared, and Whitehouse had a similar experience, Winfield had no definite success with a case which he treated. Gottheil also reported a failure. Schindler, however, claimed good results with radium treatment of xanthoma palpebrarum. The passage of time has not clarified the confusion. Siemens recently tried out radiation thoroughly in an intractable case of xanthoma multiplex. Neither superficial nor deep roentgen therapy, the
surface application of radium, nor intravenous thorium-X affected
the progressive course of the disease. MacKee treated one case of
xanthoma tuberosum, one of xanthoma planum, and another of
xanthoma diabeticorum with roentgen rays without success. He
also failed to secure regression in a case of xanthoma palpebrarum
which he treated with beta rays of radium. Sosman treated one
doubtful and two probable cases of Christian's-Schüller's disease
with roentgen rays. Although dietary treatment had produced no
change in the skull defects in these cases the roentgen treatment
was promptly followed by repair. In the series of cases of primary
xanthoma of the breast reported herewith the two tumors which
were irradiated were certainly moderately radiosensitive. In Case
1, which received preoperative interstitial radium treatment, the
dimination in the size of the tumor is well illustrated by comparison
of Figs. 1 and 2, which show the lesion before and after radiation.
In Case 2 the tumor distinctly diminished in size under preopera-
tive roentgen treatment.

In the face of the fact that there seems to be no way of diagnos-
ing primary xanthoma of the breast clinically, the proper procedure
when such a lesion is suspected is biopsy. If the yellow color of the
gross specimen does not make the diagnosis of primary xanthoma
sure, however, it is probable that not much help will be obtained
from frozen sections. Since primary xanthoma of the breast has
not been described before, except for Cheatle's brief report of his
case, in which the diagnosis was suggested by the yellow color of
the gross specimen and was confirmed by routine sections, no
observations as to experience with frozen section diagnosis are
available. Frozen sections were not done in the three cases of
primary xanthoma which are the subject of the present report.
From his knowledge of their histology the writer suspects that it
would be very difficult indeed to distinguish in frozen sections these
tumors from certain large-celled types of carcinoma of the breast.
In such a dilemma the surgeon would have no alternative but to
proceed with radical mastectomy.

In the diagnosis of secondary xanthomatous degeneration in
true neoplasms, inflammatory processes, and traumatic fat necrosis
of the breast, frozen sections are invaluable. Here the general
histologic structure of the lesion should distinguish it from car-
cinoma. Traumatic fat necrosis in the repair stage may offer very
great difficulty, however. Keynes reports that in his case the
lesion was mistaken in the frozen section for carcinoma and a
radical mastectomy performed. The section showed "large polyhedral cells apparently lying in alveoli. These cells were not quite like the usual type of carcinoma, being even larger than the unshrunk cells seen in fresh sections; but the appearance was not recognizable as anything else, and the diagnosis was taken to be confirmed." The case of traumatic fat necrosis (Case 6) included in the present study was diagnosed by frozen section.

**Summary**

Xanthomas in general have been discussed, and tumors of the breast containing xanthoma cells have been classified as follows:

A. Primary xanthoma: a very rare tumor composed wholly of xanthoma cells and arising as a local manifestation of the syndrome of xanthomatosis.

B. Secondary xanthomatous degeneration, frequently encountered in (1) true neoplasms, (2) inflammatory processes, and (3) traumatic fat necrosis.

Three cases of primary xanthoma of the breast, and illustrative cases of secondary xanthomatous degeneration occurring in fibroadenoma, in chronic breast abscess, and in traumatic fat necrosis in the breast have been described.

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