The modern Imaging of fat necrosis: a "great mimicker" in the breast and beyond.

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Learning objectives

To review clinical features, aetiology, pathogenesis and pathology of fat necrosis occurring in the subcutaneous tissue (after trauma, in the newborn, and in association with pancreatic disease) and in the breast, and to describe its Imaging features, with special emphasis to differential diagnosis with cancer of the abdominal and mammary forms.
Background

1) CLINICAL FEATURES OF FAT NECROSIS

A) POST-TRAUMATIC SUBCUTANEOUS FAT NECROSIS

Often following an extensive, slowly resolving haematoma, fat necrosis and atrophy manifest as a subcutaneous defect, while pseudolipoma is a mass with the consistency of normal adipose tissue [1,2]. Usually asymptomatic, in rare cases all these conditions are associated with local chronic pain (sometimes requiring surgery), likely related to post-traumatic reflex sympathetic dystrophy-like symptoms [3].

In the nodular cystic variant, the necrotic fat is encapsulated by a thin rim of fibrous tissue and may undergo calcification and pseudomembranous transformation; in some cases its size may be relevant [4-6].

B) SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

Most often occurring in the shoulders, back and buttocks [7], subcutaneous fat necrosis of the newborn is characterized by the presence of painful, firm, indurated, erythematous nodules (Fig. 1) and plaques [8]. Hypercalcaemia (developing weeks or months after the onset of the skin lesions) and - in rare cases - thrombocytopenia may accompany this disorder.

Subcutaneous fat necrosis is per se a self-limiting condition: the skin lesions resolve spontaneously within a few months [9], seldom if ever progressing to atrophy, scarring or ulceration [8]. If not adequately treated, hypercalcaemia can however be life-threatening [10].

C) PANCREATIC FAT NECROSIS

In 2 to 3 percent of all patients with acute pancreatitis, but also in those with chronic pancreatitis or pancreatic carcinoma (predating, concurrently with, or lagging behind the pancreatic disease [11,12]), erythematous or red-brown subcutaneous nodules develop (Fig. 2), with a tendency to show central softening and sometimes to spontaneously ulcerate and discharge thick oily material [13]. The usual sites are the distal parts of the lower extremities but involvement of breasts, buttocks, thighs, and abdomen has been described [11]. These features are shared by the lesions occurring in patients with erythema nodosum, erythema induratum, and the panniculitides associated with lupus erythematosus, Weber-Christian disease and alpha-1 antitrypsin deficiency [14]. Subcutaneous fat necrosis usually disappears, without specific treatment, after improving of acute pancreatitis.

Besides the skin, necrosis may affect the periarticular fat tissue, causing the PPP (pancreatitis, panniculitis and polyarthritis) syndrome [11,15], which may follow a chronic
course with a radiographic joint damage and a poor response to anti-inflammatory drugs [15].

Infrequently, in patients with pancreatic disease necrosis may also be found in the intramedullary osseous fat [16,17] and in the mediastinal fat [18].

D) BREAST FAT NECROSIS

Breast fat necrosis typically presents as a superficial, usually periareolar small, painless, ill-defined mass [19]. In a minority of cases bruising and tenderness, skin tethering or dimpling, or nipple retraction are associated. Fat necrosis may enlarge, remain unchanged, regress, or resolve [20,21].

2) ETIOLOGY AND PATHOGENESIS OF FAT NECROSIS

A) POST-TRAUMATIC SUBCUTANEOUS FAT NECROSIS

Necrosis and pseudolipoma may occur in the subcutaneous fat following (with a two-years mean interval) blunt injury, surgery, and minor procedures or injections [1,3,22].

A direct mechanical effect (the impact-induced prolapse of adipose tissue through the interrupted fascia) or the result of preadipocyte differentiation and proliferation mediated by inflammatory changes (cytokine release following traumatic hematoma formation and fat necrosis [1,23]) are the most trusted pathogenetic hypotheses.

The nodular cystic fat necrosis seems to be related to a rapid ischemia triggered by trauma, with subsequent fibrous capsule formation [5,6].

B) SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

Mechanical trauma during delivery (as suggested by the preferred body locations: [7,10]), cold (similar lesions are observed in children in whom hypothermia is induced to reduce the neurologic sequelae of birth asphyxia [24] or prior to cardiac surgery [25]) or hypoxaemia [8] may cause necrosis of the immature fat of the newborn. The adipose tissue of neonates has a higher ratio of saturated (palmitic and stearic acids) to unsaturated fatty acids (oleic acid) than the adult's [26], causing the melting point of the fat to be high, what in turn might explain its tendency to undergo crystallization and subsequent necrosis under stress condition [25] and in a low local temperature [7].

As for the subsequent hypercalcaemia, the most likely mechanism seems to be an increase in the intestinal absorption of calcium and in the bone turnover caused by high levels of 1,25-dihydroxyvitamin D [7,27] produced in excess by the activated macrophages infiltrating the foci of subcutaneous fat necrosis, like in other granulomatous diseases (sarcoidosis, tuberculosis).

C) PANCREATIC FAT NECROSIS
Although it can be found in the areas of subcutaneous fat necrosis [28,29], pancreatic lipase alone is no longer considered the responsible of this phenomenon [30], and cases of fat necrosis with normal serum lipase levels have been documented [31]. Pancreatic enzymes released during pancreatitis, such as trypsin, may increase the microvascular permeability, thus allowing lipase to degrade normal fat [32,33].

Besides being a process secondary to acute pancreatitis, adipose tissue necrosis contributes to the generation of mediators potentially involved in the induction of the systemic inflammatory response [34].

**D) BREAST FAT NECROSIS**

In some cases resulting from accidental trauma, breast fat necrosis is most commonly seen after surgery or radiation therapy [21,35]. Its incidence is growing due to the number of surgical procedures (such as autologous tissue reconstruction and mammoplasty [36]) and of intra-operative radiotherapy [37] performed nowadays: fat necrosis occurs in up to one-quarter of patients following post-lumpectomy breast irradiation [38].

**3) PATHOLOGY OF FAT NECROSIS**

**A) POST-TRAUMATIC SUBCUTANEOUS FAT NECROSIS**

Both fat necrosis and pseudolipomas are superficial to the musculofascial system. Histological examination of the mass-forming lesions reveals noncapsulated (except the nodular cystic fat necrosis) benign adipose tissue [1].

**B) SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN**

A cavity can be observed in the fat tissue, filled with necrotic debris and - often - calcareous material, whose wall is constituted by a layer of fibrous granulation tissue with inflammatory infiltrate containing macrophages (Fig. 3), in a pattern similar to a foreign body reaction [39].

**C) PANCREATIC FAT NECROSIS**

Necrosis is revealed by "ghost" adipocytes, which demonstrate a thick shadowy wall, absence of nuclei and finely granular basophilic birefringent cytoplasmic material (Fig. 4) deriving from saponification of fat [40-42].

**D) BREAST FAT NECROSIS**

The early stage of fat necrosis is characterized by degenerative changes in adipocytes accompanied by haemorrhage, followed over several weeks by demarcation of the necrotic area through infiltration of histiocytes and multinucleated giant cells (Fig. 5). The degenerated erythrocytes conglomerate among the fat released by the necrotic adipocytes, giving rise to "myospherulosis," which is characteristic of fat necrosis. In the late stage of fat necrosis hemosiderin deposition and development of fibrosis are seen,
leading to scar formation. Cystic degeneration may occur, resulting in a cavity containing oily fluid, in whose walls calcifications frequently develop; degenerated fat or oil may persist for months or years in a cyst surrounded by fibrosis [19, 21, 35].
**Fig. 0:** Indurated subcutaneous nodules on the left shoulder and back (arrows) of a 11-days old girl who underwent hypothermic cardiac surgery.

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Fig. 0: Multiple erythematous to brownish nodules on both lower legs of a 50-years old man with alcohol-induced acute pancreatitis.

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**Fig. 0:** 5-days old boy with subcutaneous fat necrosis (Hematoxylin-eosin stain). Panniculitis with sparring of the dermis and epidermis (A: 40x). Mixed inflammatory infiltrate (histiocytes, lymphocytes, neutrophils, eosinophils), with cleft-like spaces (arrow) suggestive of dissolved crystals at the periphery of some of the fat cysts (B: 400x).

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Fig. 0: Pancreatic subcutaneous fat necrosis (Hematoxylin-eosin stain). Diffuse fat necrosis and fine granular basophilic material deposited in the subcutis (A: 40x). Ghost-like fat cells with thick shadowy walls and no nuclei (B: 200x).

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Fig. 0: Necrotic adipocytes with some infiltration of inflammatory cells 2 months after breast trauma in a 62-years old woman.

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1) POST-TRAUMATIC SUBCUTANEOUS FAT NECROSIS

Two possible sonographic appearances of fat necrosis of the extremities and torso have been reported: a well-circumscribed isoechoic mass with a hypoechoic halo and a poorly defined hyperechoic region [43].

On MRI examinations pseudolipomas appear as focal fatty masses with no capsule or contrast enhancement [2]. A bright linear signal on fat-saturated both T1- and T2-weighted images, likely representing scar tissue, can rarely be seen within pseudolipomas [3].

2) SUBCUTANEOUS FAT NECROSIS OF THE NEWBORN

Ultrasound and MRI features are similar to the findings of non-mass forming post-traumatic fat necrosis; Imaging studies, however, are not routinely performed in this condition.

3) PANCREATIC FAT NECROSIS

As for its typical subcutaneous manifestation, pancreatic fat necrosis is not distinguishable, at ultrasound and MRI, from post-traumatic fat necrosis.

Mass-like fat necrosis, due to coalescence of multiple foci, has however been described within the abdominal wall [44] and, more often, inside the abdominal cavity (especially in the root of the transverse mesocolon [40]), in some cases mimicking at CT - according to its location - pancreatic (Fig. 6) [45] or renal malignancy [46] or retroperitoneal liposarcoma (Fig. 7) [47].

Differential diagnosis with cancer is also necessary in the case of intramedullary fat necrosis, whose radiographic and CT features (multiple osteolytic lesions) resemble those of metastases [16,17].

4) BREAST FAT NECROSIS

The Imaging features of fat necrosis are mainly determined by the extent of the associated fibrosis, along with the inflammatory reaction, the amount of liquefied fat and the presence of calcifications.

A) MAMMOGRAPHY

When little or no fibrotic reaction occurs, fat necrosis appears as a typically benign radiolucent oil cyst on mammography (Fig. 8), with linear and curvilinear calcifications developing early and central calcifications visualized later (Fig. 9). Calcifications are
usually smooth and round or curvilinear; they may however have a more worrisome appearance, including branching, rodlike, or angular calcifications [21,48]. Radiolucent necrotic fat circumscribed by thickened, irregularly dense walls can be seen in the presence of a more intense fibrotic reaction; if the reparative fibrosis replaces all of the necrotic fat, an irregular, dense, spiculated mass or a focal asymmetry - both features sometimes difficult to be distinguished from breast cancer (Fig. 10) - may appear on mammograms [21,36].

B) ULTRASOUND

The sonographic features of fat necrosis are varied and less specific than mammographic findings [21,49].

Fat necrosis may present as a solid iso- or hyperechoic mass (this latter - Fig. 11A - being the most common feature), a complex mass with mural nodules or with echogenic bands shifting in orientation with changes in patient position (which are supposed to represent the interface between the lipid and the serous-hemorrhagic components of fat necrosis), an anechoic mass with posterior acoustic enhancement or with shadowing (Fig. 11B) [36,50,51]. The margins range from well circumscribed to indistinct to spiculated.

C) MRI

MRI may be helpful in making the diagnosis of fat necrosis, especially if the internal signal characteristics are identical to those of the adjacent adipose tissue and no evidence of enhancement is seen after the administration of IV paramagnetic contrast material [21,36].

Nevertheless, fat necrosis may mimic malignancy on MRI on the basis of signal intensity, morphology and contrast kinetics [21]. Necrotic fat may show a signal intensity lower than usual on non-saturated T1-weighted MRI, due to its hemorrhagic and inflammatory content; like on mammography (Fig. 12A), masses and regions of architectural distortion are often seen because of fibrosis (Fig. 12B). Moreover, after paramagnetic contrast material fat necrosis - depending on the intensity of the inflammatory process - may show enhancement [36], which can be focal or diffuse, homogeneous or inhomogeneous; in some cases a rim enhancement with a central non-enhancing area is seen. As for its kinetics, enhancement may be slow to rapid; sometimes a washout curve is present [36,52].

A slow diffusion of water, making differential diagnosis towards malignancy difficult, is shown by breast fat necrosis at diffusion-weighted MRI (Fig. 12C), probably because of the abundance of extra-cellular hydrophobic lipid molecules [53].
Fig. 0: A solid well-circumscribed mass, apparently growing from the head of the pancreas, is demonstrated (arrows) at CT scan (A), T2-weighted turbo spin-echo MRI (B) and T1-weighted gradient-recalled-echo MRI (C). No enhancement is observed after iodinated contrast medium at CT (A) or after mangafodipir at T1-weighted gradient-recalled-echo MRI (D): this latter image, however, clearly demarcates the lesion from the normal pancreas. Fat necrosis was found at surgery in this man, suffering four months earlier of acute pancreatitis.

**Fig. 0:** A septated, thin-walled, mostly fatty (with scattered foci of mildly enhancing soft tissue components and areas of hemorrhage) lesion is demonstrated in the lesser sac, mimicking at CT a retroperitoneal liposarcoma. Fat necrosis was found at surgery in this man, suffering several months earlier of acute pancreatitis.

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**Fig. 0:** A well-circumscribed radiolucent area surrounded by a thin capsule (white box) is seen at a lateromedial view in the right breast of a 59-years old woman. The findings are consistent with a benign oil cyst.

Fig. 0: (A) Curvilinear calcifications (arrow) are seen in the peripheral portion of a radiolucent mass with thin rim (arrowheads) in the left breast of a woman who four months earlier underwent surgical biopsy. Findings are consistent with early stage of fat necrosis. (B) In a different patient who nine years earlier underwent segmental mastectomy, coarse calcifications in both peripheral and central portions of mass-like fat necrosis developed.

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Fig. 0: (A) A dense, spiculated mass that had increased in size since prior mammogram is seen on a mediolateral oblique view in a woman who six years earlier underwent right segmental mastectomy. (B) In a different patient who ten months earlier suffered a blunt breast trauma, a high-density, spiculated mass (arrow) is observed. Biopsy revealed findings consistent with fat necrosis in both patients.

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**Fig. 0:** (A) A hyperechoic mass (arrows) is seen at ultrasound examination in correspondence with a new palpable mass in a woman with history of invasive ductal carcinoma surgically removed in that same breast. Biopsy revealed fat necrosis. (B) An anechoic mass in a woman with recent (one week) history of blunt breast trauma.

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**Fig. 0:** Some architectural distortion can be seen on a mediolateral oblique mammogram (A) of a 67-years old woman. MRI examination (B) shows a spiculated mass, with a peripheral enhancing portion circumscribing a non-enhancing core, whose diffusion (C) is very slow (ADC: $1.23 \times 10^{-3}$ mm$^2$/sec). These findings are consistent with breast malignancy; fat necrosis was however found at biopsy.

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Conclusion

Post-traumatic and neonatal subcutaneous fat necrosis are usually identified on the basis of history and age of the patients. On the other hand, differentiating from malignancy some cases of fat necrosis induced by pancreatic disease and many forms of breast fat necrosis may be very challenging, even with the most recent Imaging methods like CT, MRI and diffusion-weighted MRI.
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References


