Fat necrosis following inadvertent subcutaneous administration of influenza vaccination

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Radiology Case. 2024 July; 18(7):46-54 :: DOI: 10.3941/jrcr.4760

Authors' contributions
Dan Li: Manuscript preparation, Graphic preparation, Table preparation,
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Consent
No. No identifying information is provided in this case report.

Ethical Statement / Human and animal rights
Not Applicable

Conflict of Interest / Disclosures
None

ABSTRACT

Fat necrosis has been commonly described in the breast as a mimic for carcinoma, however only rare cases of subcutaneous fat necrosis in the extremities have been reported. We show the case of a 41-year-old woman who presented with fat necrosis after a routine influenza vaccination. Subcutaneous fat necrosis was diagnosed based on the ultrasound, radiographic, and magnetic resonance imaging appearance of the lesion. Identification of the characteristic imaging features of subcutaneous fat necrosis may benefit patients by expediting diagnosis and preventing unnecessary biopsies and surgical procedures.

CASE REPORT

BACKGROUND

Fat necrosis has been commonly described in the breast as a mimic for carcinoma, however only rare cases of subcutaneous fat necrosis in the extremities have been reported. We show the case of a 41-year-old woman who presented with fat necrosis after a routine influenza vaccination. Identification of the characteristic imaging features of subcutaneous fat necrosis may benefit patients by expediting diagnosis and preventing unnecessary biopsies and surgical procedures.

CASE REPORT

A 41-year-old female presented to clinic complaining of swelling and ecchymoses about the left deltoid 24 hours after receiving the quadrivalent influenza vaccination (Afluria). She had no history of allergies to influenza vaccination, nor did she have any other history of panniculitis, though she did reportedly have a history of deltoid abscess that resolved many years ago. Her other medical history was non-contributory, notable for obesity and major depressive disorder. She continued to complain of a bump four months after her initial vaccination. Physical exam was notable for a 3 x 2 x 1 cm firm mass in the left upper arm with mild surrounding ecchymoses (Figure 1). An ultrasound was obtained, which demonstrated two ovoid anechoic structures with posterior acoustic shadowing within the subcutaneous fat (Figure 2). Subsequent contrast-enhanced magnetic resonance imaging (MRI) demonstrated two foci with fat signal intensity with enhancing fibrinous infiltration within the subcutaneous fat (Figure 3). Concurrently a radiograph of the humerus was obtained, which showed soft tissue stranding within the subcutaneous fat without calcifications (Figure 4). The imaging findings were characteristic of fat necrosis and

no further imaging or biopsy was recommended. Upon clinic follow-up eight months after the initial injection, the patient continued to have a firm palpable nodule without tenderness or change in size.

DISCUSSION

Etiology and Demographics

Fat necrosis at a histopathological level is a focal panniculitis, most often described in the breast tissue after trauma or instrumentation or in association with systemic inflammatory disorders. There are multiple histological subtypes of panniculitis; the subtype related to injection is classified as traumatic panniculitis which is defined by changes in subcutaneous fat related to physical or chemical insult, which results in adipocyte apoptosis or necrosis. Release of cytosolic components may then trigger an inflammatory reaction leading to the signature imaging findings. Early traumatic panniculitis is characterized by non-specific inflammatory response with increased lymphocyte and macrophage activity. In later stages, fibrotic replacement of damaged fat cells occurs, which may also be associated with dystrophic calcium deposition [1]. An oil cyst, which contains macroscopic fat, may form at the center of necrosis which is walled off by a fibrinous shell [2]. Fat necrosis related to injection may be more common in individuals who frequently receive intramuscular or subcutaneous injections [3]. Additionally, injection related necrosis may be more common in middle aged women and teenage boys [4].

Unintended subcutaneous injection of intramuscular injections may increase the chance of complications such as fat necrosis, as well as alter the kinetics of the drug being injected. Inadvertent subcutaneous injection increases the incidence of local reaction due to relatively poor blood supply of subcutaneous fat relative to the muscle [5]. Injection technique should be adjusted depending on the body habitus of the patient. For female patients > 90kg, a needle up to 1.5 inches in length may be required to ensure intramuscular administration; the weight of the patient in this report was 112 kg, putting her at elevated risk of inadvertent subcutaneous injection with a shorter needle [6].

No cases of fat necrosis specifically after influenza vaccination have been reported in prior literature. At least one case of subcutaneous fat necrosis after COVID-19 vaccination (Astra Zeneca), also an intramuscular medication, has been reported [7].

Clinical and imaging features

Patients present clinically with non-specific soft tissue masses and ecchymoses on physical exam. Often, the patient does not recall any history of trauma or clear inciting event. There are limited documented cases of fat necrosis in the subcutaneous tissue. However, the appearance of fat necrosis in the breast has been well-characterized.

The ultrasound appearance of subcutaneous fat necrosis is variable and may present as an anechoic cyst with posterior acoustic shadowing, hypoechoic mass, solid mass, or complex cyst (sometimes including mural nodules). Increased echogenicity of the subcutaneous fat is seen in 27% of cases, representing inflammatory changes [8]. In this case, the area of concern was anechoic with minimal internal echogenicity and posterior acoustic shadowing, in keeping with an oil cyst at the center of necrosis [9].

The radiographic appearance of fat necrosis is non-specific, though its presence is suggested if peripheral calcifications are visualized in a patient with history of insult or trauma to the corresponding area. Computed tomography (CT) imaging may show liquified low attenuation fat with surrounding hyperattenuating bands of fibrous tissue, which may enhance after contrast injection [2]. As with radiography, CT may show peripheral calcifications in later stages of fat necrosis.

The MRI appearance of fat necrosis in the breast classically manifests as a central non-enhancing STIR hypointense focus ("black hole sign") on fat suppression sequences, surrounded by variable amounts of enhancing inflammation [2]. Surrounding T2 hyperintensity may be present, representing inflammatory edema.

The MRI appearance of fat necrosis is not well-documented in the extremities compared to the breast. Lai et al. reviewed five cases of biopsy-proven fat necrosis in the extremities and gluteal region, finding only two cases to have the typical intra-breast appearance of fat-intensity globular lesion surrounded by fibrinous tissue. This review was complicated by the fact that several of the cases of necrosis occurred within a lipomatous lesion, so this report may be of limited use in assessing cases of injection-related fat necrosis [10].

Tsai et al. evaluated 13 cases of pediatric fat necrosis after trauma to the lower extremities and gluteal region. These cases exhibited heterogenous T1/T2 sequence findings, but all cases were limited to the subcutaneous tissue and did not exhibit a discrete mass. These findings contrast with the typical "black hole" sign seen on breast MRI and with the case presented in this report. Of the 13 pediatric cases evaluated in this study, 10 patients had lesions at the anterior tibia. It is possible that the mechanism of injury (i.e. blunt trauma to the shin in pediatric patients versus secondary to injection) may affect the MRI appearance of the lesion [11].

Yet another study conducted by Lopez et al. examined 12 cases of traumatic fat necrosis in the extremities. In contrast to the findings of Tsai et al., Lopez et al. noted a focal signal void on STIR images in several cases with surrounding T2 hyperintensity, consistent with the classic MRI appearance of fat necrosis in breast tissue [12]. Given the discrepancies noted between these case series, more research would be helpful to elucidate the typical appearance and common variances of subcutaneous fat necrosis in the extremities.

Treatment and Prognosis

The treatment of subcutaneous fat necrosis depends on the underlying etiology. Prevention is crucial, starting with

proper needle length selection relative to body habitus for intramuscular injections. Due to the rarity of injection-related fat necrosis, no standardized diagnostic or surgical evaluation has been proposed for patients presenting with this condition. Fat necrosis in the breast is treated conservatively, with surgery generally only performed for symptoms or concomitant complications, such as infection, skin necrosis, or hematoma [13]. A similarly conservative approach might be considered in management of fat necrosis of the extremities, consisting of lesion monitoring, either with physical exam or ultrasound, reassurance, and symptom management. In cases where the patient experiences significant pain or distress, surgical excision can be performed. Lesions that are continuously enlarging should be biopsied to rule out malignant lipomatous lesions. There is no known intrinsic malignant potential related to subcutaneous fat necrosis. The natural course of subcutaneous fat necrosis in the extremities is not known, though in the case of breast fat, resolution is often seen within 10 years without intervention [14].

Differential Diagnosis

The differential diagnosis of suspected subcutaneous fat necrosis in the extremities includes other lipid-rich lesions, including lipomatous lesions (lipoma, angiolipoma, liposarcoma), alpha-1-antitrypsin deficiency associated panniculitis, pancreatitis associated panniculitis, and membranous fat necrosis.

Lipoma

Lipomas follow subcutaneous fat signal on all sequences including homogenous T1 hyperintensity with loss of signal on fat saturated or STIR sequences. There is typically minimal if any non-fatty intralesional components, excepting thin bands of muscle and thin septa < 2 mm. There is no enhancement of intralesional components, nor should there be foci of T2 hyperintensity relative to the surrounding subcutaneous fat signal. The presence of these characteristics raise suspicion for atypical lipoma or liposarcoma [15]. The presence of fat necrosis is non-specific and may be seen within benign lipomas.

Atypical Lipoma/Liposarcoma

Atypical lipoma and well-differentiated liposarcoma are synonyms used to describe low grade lesions on the spectrum of liposarcoma. Features concerning for liposarcomatous lesions include size > 5 cm or rapid size change, thickened or nodular septa, associated soft tissue/non-adipose masses, foci of T2 signal, or areas of focal enhancement [15,16]. In some cases, irregular fat necrosis within a lipoma may resemble non-adipose or enhancing masses within the lesion, resulting in false positive diagnoses. While MRI is almost 100% sensitive for liposarcoma, lipomas with intralesional components may occasionally be mistaken for liposarcomas, reducing the specificity.

Other rare lipoma variants may also be mistaken for atypical lipomas/well-differentiated liposarcomas on imaging or histopathological examination. These include chondroid lipoma, hibernoma, fat necrosis (as above), osteolipoma, lipoleiolipoma, and angiolipoma.

Alpha-1-antitrypsin (AAT) deficiency panniculitis

Both AAT deficiency and pancreatitis associated panniculitis may present with subcutaneous and, less commonly, mesenteric fat necrosis.

Alpha-1-antitrypsin deficiency results in inability to control neutrophil elastases resulting in damage to alveolar walls which then results in pan-lobular pulmonary emphysema. Additionally, build-up of abnormal alpha-1-antitrypsin proteins can result in hepatotoxicity, eventually leading to cirrhosis. Cutaneous manifestations may be secondary to overactivity of neutrophil proteases in the subcutaneous fat due to decreased AAT activity.

The clinical presentation is characterized by multifocal subcutaneous nodules and/or ulcerations, often associated with minor traumas. In the case of AAT deficiency, the cutaneous panniculitis may manifest before hepatic and pulmonary symptoms and therefore a high index of suspicion is required to make the diagnosis [17].

There are no specific subcutaneous radiological findings that distinguish AAT deficiency associated panniculitis from other etiologies of fat necrosis.

Pancreatitis associated panniculitis

Acute pancreatitis may occur secondary to a variety of etiologies, most commonly gallstones and excessive alcohol use. Pancreatic enzymes, such as lipase and amylase, that are released secondary to pancreatic disease may cause lipolysis in the subcutaneous tissue and subsequent fat necrosis.

Pancreatitis associated panniculitis classically presents with erythematous nodules, predominantly in the lower extremities and buttocks. In up to half of cases, the cutaneous findings precede the abdominal manifestations of pancreatitis [18].

As with AAT deficiency associated panniculitis, imaging is non-specific. Radiologic studies may be helpful at making the diagnosis by identifying other features associated with the disease (e.g. body imaging for acute pancreatitis).

Membranous fatty necrosis

Membranous or lipomembranous fat necrosis (LPFN) is a subtype of fat necrosis characterized by replacement of adipocytes with an undulating membrane which often forms cysts. These pseudomembranes may form secondary to failure of phagocytosis, though a variety of mechanisms have been proposed. LPFN may occur in subcutaneous fat secondary to a wide range of systemic panniculitides [19]. In the breast, LPFN is most often secondary to radiation treatment [20].

TEACHING POINT

Fat necrosis may occur after mild physical or chemical insults to the subcutaneous fat, including after inadvertent

subcutaneous administration of influenza vaccination. The imaging appearance is variable, though successful imaging-based diagnosis may be useful to prevent unnecessary biopsy and/or surgical procedure. The prognosis of fat necrosis is good and is likely self-resolving.

QUESTIONS

Question 1: Which of the following describes the classic "black hole" sign on breast MRI?

1. STIR Hypointense oval lesion within the breast fat (applies)
2. Laminar T2 intensity within the breast fat
3. Abnormal nipple enhancement with deep linear clumped enhancement
4. Non-mass enhancement with ring-like internal enhancement
5. Slow contrast enhancement with non-enhancing internal septations

Explanation:

1. The "black hole" sign on breast MRI describes a markedly hypointense area compared to the surrounding fat, which is only partially suppressed. This occurs due to narrow distribution of T1 relaxation time within an area of necrotic fat.
2. Laminar T2 intensity within the breast may be associated with fat necrosis, sometimes surrounding a focal area of necrosis; this may be due to edema or fibrous changes.
3. Abnormal nipple enhancement may suggest Paget disease of breast. Associated clumped enhancement is suspicious for ductal carcinoma in situ in association with Paget disease.
4. Ring-like internal enhancement is specific for breast malignancy, most often ductal carcinoma in situ.
5. Slow contrast enhancement with a persistent delayed phase and internal septation is suggestive of breast fibroadenoma.

Question 2: For a female patient weighing >90 kg, what length of needle is recommended to insure at least 5 mm of muscular penetration with injection?

1. 5/8 inch
2. 1 inch
3. 1.5 inch (applies)
4. 2.0 inch
5. Any size of available needle is acceptable

Explanation:

1. 5/8 inch needles are recommended for women who weigh less than 60 kg.
2. 1 inch needles are acceptable for all male patients. For female patients between 60 and 90 kg, an 1 inch needle is sufficient.
3. For women greater than 90 kg, a 1.5inch needle is recommended to ensure intramuscular administration. [Injection technique should be adjusted depending on the body habitus of the patient. In the case of a woman weighing > 90kg, a needle up to 1.5 inches may be required to ensure intramuscular administration.]
4. 2 inch needles are not routinely used for intramuscular injection.
5. The smallest size of needle that ensures muscular penetration should be used when administering an intramuscular vaccination.

Question 3: Which of the imaging characteristics on MRI make a fat containing lesion more likely to be a liposarcoma, as opposed to a benign lipoma? Select all that apply.

1. T2 enhancing hyperintense foci within the lesion (applies)
2. Size greater than 5 cm or rapid change in size (applies)
3. Thin septations < 2 mm
4. Areas of necrosis
5. Thick or nodular enhancing septa (Applies)

Explanation:

1. Features that increase concern for atypical lipoma or liposarcoma include: thickened or nodular septa, associated soft tissue/non-adipose masses, foci of T2 signal, or areas of focal enhancement. [Features concerning for these liposarcomatous lesions include thickened or nodular septa, associated soft tissue/non-adipose masses, foci of T2 signal, or areas of focal enhancement]
2. See explanation 1.
3. Thin septations alone may appear in lipoma and do not raise concern for liposarcoma in the absence of nodularity or enhancement. [Lipomas do not feature enhancement of intralesional components, nor are there foci of T2 hyperintensity relative to the surrounding subcutaneous fat signal.]
4. Areas of necrosis may be seen in both lipomas and liposarcomas, as well as in other pathology, such as subcutaneous fat necrosis. The presence of fat necrosis alone does not raise suspicion of liposarcoma. [The presence of fat necrosis is non-specific and may be seen within benign lipomas.]
5. See explanation 1.

Question 4: Which of the following are manifestations of Alpha-1-antitrypsin deficiency?

1. Panlobular emphysema (applies)
2. Type 1 Diabetes
3. Necrotizing panniculitis (applies)
4. Increased serum lipase
5. Hepatic cirrhosis (applies)

Explanation:

1. Excessive activity of neutrophil elastase results in damage to the lower respiratory tract, often with a basal predominance due to gravity-dependent blood flow. [Alpha-1-antitrypsin deficiency results in inability to control neutrophil elastases resulting in damage to alveolar walls which then results in pan-lobular pulmonary emphysema.]
2. Patients with cystic fibrosis may develop similar symptoms to type I diabetes due to scarring of the pancreas which results in insulin deficiency.
3. Excessive activity of neutrophil elastase, which are degraded by A1AT normally, can cause multifocal subcutaneous fat necrosis. [Cutaneous manifestations may be secondary to overactivity of neutrophil elastase in the subcutaneous fat due to decreased AAT activity.]

4. Greater than threefold increase in serum lipase is a marker of acute pancreatitis.

5. AAT deficiency results in abnormal synthesis and folding of proteins, which the aggregate in the liver, resulting in hepatotoxicity. [Build-up of abnormal alpha-1-antitrypsin proteins can result in hepatotoxicity, eventually leading to cirrhosis.]

Question 5: Which of the following are true regarding acute pancreatitis?

1. Patients classically present with right lower quadrant pain
2. Serum lipase may be elevated (applies)
3. The most common cause is scorpion bite
4. It is the most common cause of subcutaneous fat necrosis
5. Cutaneous manifestations may precede intra-abdominal findings (applies)

Explanation:

1. Acute pancreatitis classically presents with epigastric pain radiating to the back.

2. One of the diagnostic criteria for acute pancreatitis is serum lipase or amylase greater than 3x the upper limit of normal. [Pancreatic enzymes, such as amylase and lipase, that are released secondary to pancreatic disease may cause lipolysis in the subcutaneous tissue and subsequent fat necrosis.]

3. The most common causes of acute pancreatitis are gallstone and alcohol-related. [Acute pancreatitis may occur secondary to a variety of etiologies, most commonly gallstones and excessive alcohol use.]

4. Pancreatitis is a rare cause of fat necrosis. The most common cause of subcutaneous fat necrosis in the extremities is most likely preceding trauma (though the specific event may not be recalled by the patient). [Fat necrosis is a focal panniculitis, most often described in the breast tissue after trauma or instrumentation.]

5. Cutaneous manifestations, such as erythematous nodules on the buttocks and lower extremities, of pancreatitis related panniculitis may present prior the intra-abdominal findings. [Pancreatitis associated panniculitis classically presents with erythematous nodules, predominantly in the lower extremities and buttocks. In up to half of cases, the cutaneous findings may precede the abdominal manifestations of pancreatitis.]

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FIGURES

Figure 1: 41-year-old female with fat necrosis of the left upper extremity following influenza vaccination.
Findings: Color photo of the patient's left deltoid. A 3 x 2 x 1 cm firm mass in the left upper arm with mild surrounding ecchymoses was noted following intramuscular influenza vaccination. This photo was taken approximately four months after the vaccination.

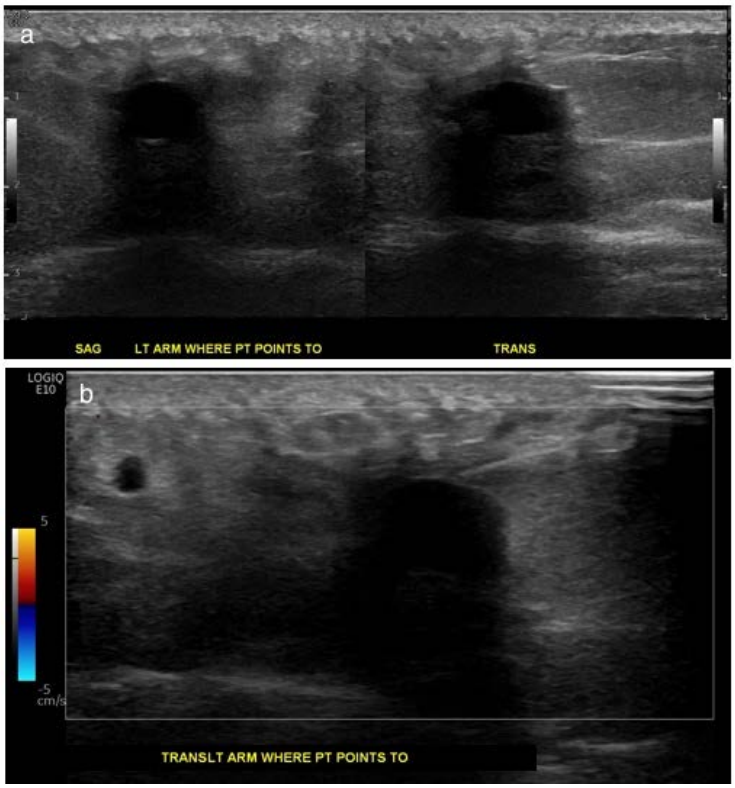

Figure 2: 41-year-old female with fat necrosis of the left upper extremity following influenza vaccination.

Findings (top to bottom):
(a) Transverse and longitudinal grayscale ultrasound images demonstrate a sub-centimeter ovoid anechoic structure with a thin echogenic rim and with posterior acoustic shadowing within the subcutaneous fat.
(b) Transverse color Doppler image shows no internal vascularity within the lesion.

Technique: GE Ultrasound, ML6-15 linear array probe

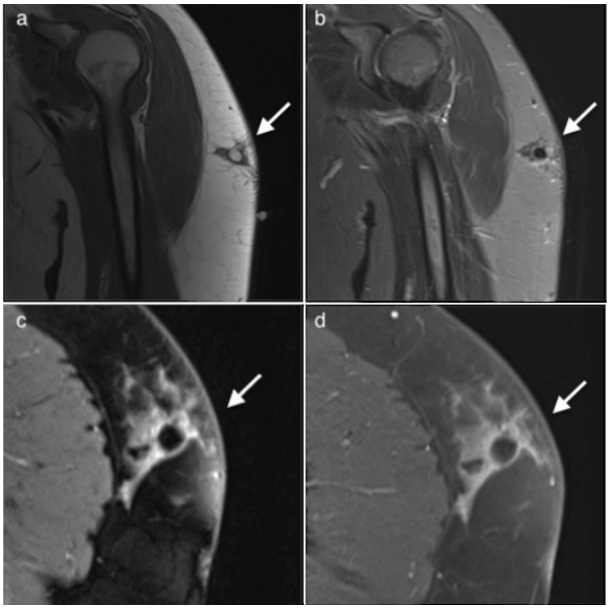

Figure 3: 41-year-old female with fat necrosis of the left upper extremity following influenza vaccination.

Findings (clockwise from top left):

(a) Coronal T1-weighted sequence demonstrates a T1 hyperintense nodule in the subcutaneous fat with surrounding T1 hypointense infiltrate. The smaller rectangular nodule is better seen on axial sequences.

(b) Coronal STIR sequence demonstrates a markedly hypointense nodule ("black hole sign") in the subcutaneous fat with surrounding hypointense infiltrate. The smaller rectangular nodule is better seen on axial sequences.

(c) Axial proton density fat suppressed sequence demonstrates two fat suppressed nodules, one round and one rectangular, with surrounding T2 hyperintensity that infiltrates the subcutaneous fat.

(d) Axial T1-weighted post-contrast sequence demonstrates two T1 hypointense non-enhancing lesions, one round and one rectangular, with enhancing inflammatory reaction in the surrounding fat.

Technique:

(a) MRI: 1.5T Siemens Aura, T1 Sequence (TR 525/TE 9.2), 4.5 mm coronal slices, non-contrast

(b) MRI: 1.5T Siemens Aura, Proton density fat suppressed (TR 3210/TE 25/TI 150), 5 mm axial slices, non-contrast

(c) MRI: 1.5T Siemens Aura, T1 Post-contrast (TR 620 /TE 11), 5 mm axial slices, 7.5 mL intravenous gadobutrol (Gadevist)

MRI: 1.5T Siemens Aura, STIR (TR 4010/TE 47/TI 150), 4.5 mm coronal slices, non-contrast

Figure 4: 41-year-old female with fat necrosis of the left upper extremity.
Findings: Soft tissue stranding within the subcutaneous fat of the lateral upper arm with no calcification or ossification.
Technique: Anteroposterior radiograph of the left humerus.

SUMMARY

Etiology	Secondary to tissue trauma, physical or chemical, within the subcutaneous fat. The exact trigger is often not identified.
Incidence	Unknown. No cases of subcutaneous fat necrosis after an influenza vaccine are recorded in the literature.
Gender ratio	Unknown.
Age predilection	Unknown, although one study noted that primarily teenage boys and middle-aged women were affected.
Risk factors	Unknown.
Treatment	None required. If symptomatic, surgical excision may be considered.
Prognosis	Good. The natural history of extremity fat necrosis is unknown, but one longitudinal study of fat necrosis within the breast suggests that most cases spontaneously resolve within 10 years. Fat necrosis does not have intrinsic malignant potential.
Findings on Imaging	XR: Nonspecific soft tissue stranding within the subcutaneous fat. In chronic cases, calcifications may be seen. US: Varied. Usually hypoechoic but may be anechoic or complex cystic. Oil cyst, if present, may be anechoic with posterior acoustic shadowing due to internal homogeneity. CT: Surrounding fibrosis, which may enhance with contrast administration. If present, oil cyst or liquefied fat follows subcutaneous fat attenuation. MRI: Spiculated or globular inflammatory fibrosis. If present, oil cyst or liquefied fat follows fat signal (STIR hypointense "black hole sign").

DIFFERENTIAL

Diagnosis	Etiology, Mechanism	Imaging
Subcutaneous Fat Necrosis	Physical or chemical trauma to adipose cells, resulting in aseptic saponification within adipose tissue.	Variable appearance in the extremities. In breast tissue, fat necrosis classically appears as a spiculated enhancing lesion, sometimes with central oil cyst.
Lipoma	Lipomas are soft tissue lesions composed almost entirely of macroscopic fat. There may normally be small septa of fibrinous tissue, blood vessels, and fat necrosis within a benign lipoma.	Homogenous ovoid lesion following fat in all sequences. Thin septa (<2mm), blood vessels, and areas of necrosis may be seen.
Atypical Lipoma/Well-differentiated liposarcoma	Multiple histological types of liposarcoma have been identified. Well-differentiated liposarcoma is the most common and most likely to be mistaken for a benign lipoma.	Thick or nodular septa, which may be enhancing. Nodular, sometimes T2 hyperintense, foci within the lipoma may be seen. Size > 5cm or rapid change in size increases the risk that a fatty lesion represents liposarcoma.
A1-antitrypsin deficiency associated panniculitis	AAT is a protein that prevents enzymes, including elastase, from acting on normal tissue. AAT deficiency results in pulmonary emphysema and hepatic cirrhosis, with increased risk of lung and hepatic carcinomas. Cutaneous manifestations may be secondary to overactivity of neutrophil proteases in the subcutaneous fat due to decreased AAT activity.	Non-specific fat necrosis on the extremities, trunk, and buttocks. Intraabdominal and pulmonary findings consistent with AAT may be seen. Cutaneous findings may precede other symptoms/ radiological signs.
Pancreatitis associated panniculitis	Acute pancreatitis may occur secondary to a variety of etiologies, most commonly gallstones and excessive alcohol use. Pancreatic enzymes that are released secondary to pancreatic disease may cause lipolysis in the subcutaneous tissue and subsequent fat necrosis.	Non-specific fat necrosis on the buttocks and lower extremities. Intraabdominal and serologic findings consistent with pancreatitis may be seen. Cutaneous findings may precede other symptoms/ radiological signs.
Membranous fatty necrosis	Associated with radiation to the breast. Pseudomembranes then form around the degenerated fat cells and areas of cell necrosis. May occur due to failure of phagocytosis after fat necrosis.	Non-specific fat necrosis. The diagnosis of lipomembranous fat necrosis is made histologically.

KEYWORDS

Influenza vaccines; adverse effects; fat necrosis; magnetic resonance imaging; computed tomography; ultrasonography; radiography; subcutaneous injection

ABBREVIATIONS

AAT = Alpha-1-antitrypsin
CT = Computed tomography
LPFN = Lipomembranous fat necrosis
MRI = Magnetic resonance imaging
US = Ultrasound