Radiological and clinicopathological features of orbital xanthogranuloma

K A Miszkiel, S A A Sohaib, G E Rose, I A Cree, I F Moseley

Abstract
Background—Orbital xanthogranuloma, a diagnosis confirmed histologically, occurs rarely in adults and children. With its characteristic macroscopic appearance the adult form may be associated with a spectrum of biochemical and haematological abnormalities including lymphoproliferative malignancies.

Method—The clinicopathological features and imaging appearances on computed tomography and magnetic resonance imaging of this condition are described in eight adults and a child.

Results—Radiological evidence of proptosis was present in seven patients. In all nine patients an abnormal infiltrative soft tissue mass was seen, with increased fat in six cases. All patients had associated enlargement of extraocular muscles suggestive of infiltration and five had lacrimal gland involvement. Encasement of the optic nerve, bone destruction, and intracranial extension was present only in the child with juvenile xanthogranuloma. Haematological and/or biochemical abnormalities were detected in seven patients and seven patients had other systemic diseases which were considered to have an immune basis. One patient subsequently developed non-Hodgkin’s lymphoma.

Conclusion—The investigation and management of orbital xanthogranulomas requires a multidisciplinary approach even though the diagnosis may be suspected clinically. Imaging delineates the extent of disease and involvement of local structures and may influence the differential diagnosis. The juvenile form may be more locally aggressive, causing bone destruction with consequent intracranial extension.

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Periorbital xanthogranuloma is a rare entity that may occur in both adults and children. Although the diagnosis may be suspected in adults from the characteristic macroscopic appearance of diffuse, yellow, plaque-like masses in the eyelid, the diagnosis is confirmed histologically. It is important to recognise adult onset xanthogranuloma since this condition can be associated with hepatosplenomegaly and systemic diseases such hyperlipidaemias, diabetes mellitus, blood dyscrasias or lymphoproliferative malignancies. As affected patients present with a spectrum of ocular symptoms and signs, including displacement of the globe and restriction of lid or eye movements, imaging of the orbit with computed tomography (CT) or magnetic resonance imaging (MRI) should generally be included as part of the clinical investigations, to assess the extent of involvement of preseptal and retrobulbar tissues before biopsy of orbital tissue for histopathology.

Subjects and methods
The clinical records and all available cross sectional imaging in eight adults and one child with histologically proved orbital xanthogranuloma were retrospectively reviewed. All patients had CT and one also had an MRI scan of the orbits. Seven of the patients were male and two were female with a mean age of 41.1 (range 3–63) years at onset of symptoms. Information regarding clinical symptoms and signs at presentation, relevant biochemical or haematological abnormalities, and subsequent treatment received in this cohort of patients is given in Table 1. The case histories of four patients are presented in detail.

CASE 1
A 63 year old man presented with a 7 month history of a sore, red, irritable right eye which had undergone intracapsular cataract extraction 19 years previously, later complicated by a retinal detachment resulting in blindness. He had arthritis and psoriasis and was being treated with simvastatin for hypercholesterolaemia associated with periocular xanthelasma. Contrast enhanced CT of the orbits was performed at the time of presentation showing the right globe to be deformed and smaller than the left, with areas of retinal calcification secondary to the previous retinal detachment. There was right proptosis and depression of the globe associated with an infiltrative, poorly defined, heterogeneous, partially enhancing soft tissue density mass containing fat and involving the right upper and lower eyelids and encircling the globe. Enlargement of the extraocular muscles and increased attenuation of the retrobulbar fat was present, but no evidence of intracranial extension or of bone abnormality (Fig 1). Biopsy demonstrated infiltration of the muscle with lymphoma: no xanthoma cells were seen. CT of the chest, abdomen, and pelvis was normal, as were bone marrow aspirate, full blood count, and erythrocyte sedimentation rate. The patient therefore received 30 Gy radiotherapy (as 15 fractions) to the right orbit.

Although there was a partial regression of clinical signs, CT at 5 months after radiotherapy showed residual abnormal soft tissue
Around the right globe with extraocular muscle involvement and proptosis. The left upper eyelid, however, now showed a similar infiltration. Chlorambucil therapy produced an initial improvement after three courses of treatment, but this was not sustained, and there was progression of involvement of the left upper eyelid (Fig 2).

The patient was noted to have bilateral mechanical ptosis secondary to excess tissues and a right hypoexotropia associated with bilateral limitation of ocular movements. There was bilateral conjunctival injection. The full blood count showed a mild eosinophilia of 0.8 × 10^9 (normal 0.01–0.4 × 10^9) and serum cholesterol was also mildly elevated at 6.6 mmol/l (normal 3.0–5.5 mmol/l). Other blood tests were normal. A right orbital biopsy showed extensive infiltration of the dermis by xanthoma cells with occasional areas of lymphoid infiltration and a few Touton giant cells. The specimens were strongly positive for CD68.

Table 1 Clinical symptoms, signs, abnormal blood tests, systemic diseases, and treatment of nine patients with orbital xanthogranuloma

<table>
<thead>
<tr>
<th>Case number, age (years), sex</th>
<th>Presenting symptoms</th>
<th>Symptom duration</th>
<th>Clinical examination</th>
<th>Abnormal blood tests</th>
<th>Systemic diseases</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 63, M</td>
<td>Sore right eye</td>
<td>7 months</td>
<td>Bilateral mechanical ptosis</td>
<td>Eosinophilia</td>
<td>Psoriasis</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>2, 52, F</td>
<td>Right orbital mass</td>
<td>12 years</td>
<td>Swollen right upper lid and yellow plaques</td>
<td>Cholesterol</td>
<td>Asthma</td>
<td>Chlorambucil surgery</td>
</tr>
<tr>
<td>3, 30, F</td>
<td>Swelling right eye and monocular diplopia</td>
<td>7 years</td>
<td>Swollen right upper and lower lids</td>
<td>RA</td>
<td>Hashimoto’s thyroiditis</td>
<td>Surgery</td>
</tr>
<tr>
<td>4, 3, F</td>
<td>Swelling right eye and proptosis</td>
<td>6 months</td>
<td>Right proptosis</td>
<td>CRP</td>
<td>Asthma</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>5, 22, M</td>
<td>Bilateral upper lid swelling</td>
<td>3 years</td>
<td>Bilateral yellow upper lid plaques and left upper lid mass</td>
<td>ESR</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>6, 38, M</td>
<td>Bilateral medial upper lid swelling</td>
<td>3 years</td>
<td>Left ptosis and bilateral firm upper lid masses and yellow plaques</td>
<td>CRP</td>
<td>Asthma</td>
<td>Surgery</td>
</tr>
<tr>
<td>7, 56, M</td>
<td>Recurrent right upper lid swelling</td>
<td>8 years</td>
<td>Right ptosis, proptosis and downward displacement right upper lid yellow mass and plaque</td>
<td>Neutrophilia</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Surgery</td>
</tr>
<tr>
<td>8, 46, M</td>
<td>Right upper and lower lid swelling with pain</td>
<td>3 years</td>
<td>Right upper lid swelling with fat prolapse</td>
<td>Neutrophilia</td>
<td>Nasal polyps</td>
<td>Surgery</td>
</tr>
<tr>
<td>9, 60, F</td>
<td>Swelling right eye</td>
<td>1 year</td>
<td>Right upper lid yellow plaques</td>
<td>Neutrophilia</td>
<td>Asthma</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

⇑ = raised; ⇓ = decreased; ESR = erythrocyte sedimentation rate; NA = not available; CRP = C reactive protein; NIDDM = non-insulin dependent diabetes mellitus; NHL = non-Hodgkin’s lymphoma.
oil red O staining of frozen sections of removed fixed tissue and overall the appearances were consistent with a xanthogranuloma (Fig 3).

CASE 2
A 52 year old man was referred with a diagnosis of a recurrent granular cell tumour of the right orbit which had been removed on two occasions over the past 12 years. He had also undergone removal of superficial cervical lymph nodes for lymph node hyperplasia. The patient had a history of chronic asthma and since he had stopped oral systemic steroid therapy the right orbital mass had regrown and was now causing protrusion of the eye, intermittent aching and watering and diplopia on upgaze. At presentation the acuity was normal but the right upper lid was swollen and indurated with slight proptosis and downward displacement and limitation of movement of the right globe. A yellowish waxy plaque was present in the skin of the left lower lid.

Orbital CT and MRI confirmed right proptosis and downward displacement of the right globe with abnormal soft tissue and fat in the upper lid, extending posteriorly around the superior part of the globe (Fig 4). The abnormal soft tissue was of intermediate low signal on T1 weighted sequences and showed contrast enhancement (Fig 5). There was enlargement of the right superior rectus muscle, which also had an irregular outline. The right optic nerve, retrobulbar fat, and lacrimal gland were normal and there was no local bone abnormality. The full blood count, urea and electrolytes, and erythrocyte sedimentation rate were normal. However, the serum IgG level was raised at 23.9 g/l (normal 5.3–16.5 g/l) but with no evidence of a paraprotein. The fasting serum cholesterol was also raised at 6.0 mmol/l (normal 3.0–5.5 mmol/l) with a normal triglyceride level.

At biopsy, a pale yellow mass was identified in the right upper eyelid and the histology was compatible with a diagnosis of xanthogranuloma, showing cells with abundant vacuolated cytoplasm filled with lipid vacuoles, Touton giant cells and a chronic inflammatory perivascular infiltrate composed of plasma cells and lymphocytes. There was focal collagen degeneration consistent with the necrobiotic form of the disorder (Fig 6). Immunohistochemistry for lymphoid markers revealed that the inflammatory component of the lesion was composed of both B and T cells with polyclonality of kappa and lambda light chain staining. Review of the original histology of the right orbital lesion, previously reported as a granular cell tumour, showed a very similar appearance to the necrobiotic xanthogranuloma, with S-100 negative xanthoma cells.

Five months later the patient underwent debulking of the right orbital lesion, with some initial improvement in position of the right eyelid and globe, but with recurrence of the orbital mass within 8 months and new swelling and fullness of the left lower lid. He underwent bilateral blepharoplasties, the left lower lid mass also being found to be necrobiotic xanthogranuloma. The masses in both the right and left orbits increased, with onset of right lagophthalmos and the patient was therefore referred for local, low dose lens sparing orbital radiotherapy.
CASE 3
A woman presented at the age of 30 years with recurrent swelling of her right eye in association with fatigue related monocular diplopia. She had initially developed swelling at the age of 23 years, involving first the upper eyelid and then the lower. At the age of 28 she underwent debulking of the right orbital lesion, which was histologically reported as xanthelasma, although the swelling rapidly recurred with greater severity. Of note in her past medical history was that she developed Hashimoto’s thyroiditis at the age of 15 years which was treated with carbimazole and propranolol and subsequently required thyroxine replacement.

At the time of new presentation, she had diffuse soft tissue swelling of her right upper lid and, to a lesser extent of the lower lid medially. Eye movements were full and there was no diplopia. The right ocular fundus and left periorbital soft tissues were normal. CT of the orbits demonstrated right proptosis with abnormal soft tissue and increased fat involving the preseptal space, predominantly of the upper lid, with some posterior extension around the globe; the lateral rectus muscle was displaced medially and enlarged, the lacrimal gland was mildly enlarged and there was no bone destruction. The full blood count, urea and electrolytes, serum cholesterol, and triglyceride levels were normal. The serum IgG level was raised (18.2 g/l) although protein electrophoresis was normal. The rheumatoid factor was raised at 18 IU/ml (normal <8 IU/ml) but the C reactive protein level was normal. The patient underwent debulking of the right upper eyelid and periorbital tissue. A large fatty mass was removed and histologically a cellular infiltrate of large foamy macrophages and frequent Touton giant cells was shown to involve fat, skin, and striated muscle. Germinal lymphoid follicles and a diffuse lymphoid infiltrate were also present and the appearances were those of xanthogranuloma.

CASE 4
A 3 year old Turkish child presented with a 6 month history of slowly progressive swelling of the right eye, associated with proptosis and incomplete eye closure. There was no significant past medical history. There was right axial proptosis but a full range of eye movements and good visual acuity. No orbital mass was
The results of haematological and biochemical investigations are not available.

CT of the orbits showed right proptosis and inferior displacement of the globe due to a large posterolateral soft tissue density mass which was slightly heterogeneous, with a lower attenuation centre. There was a single small radio-opaque fleck within it, which may have represented a small calcified or haemorrhagic component. The right optic nerve and lateral rectus were displaced medially and the superior aspect of the nerve was encased posteriorly. The superior rectus muscle could not be defined separately from the mass, suggesting infiltration. There was sclerosis and irregular erosion of the greater wing of the right sphenoid and superior orbital margin with a suggestion of early intracranial extension. The appearances had progressed from a CT performed 6 months earlier (Figs 7 and 8).

The patient underwent anterior orbitotomy and a fatty mass situated above the lateral rectus and lacrimal gland was removed, this showing features of juvenile xanthogranuloma—a cellular mass containing giant cells, histiocytes and an abundance of intracytoplasmic and extracytoplasmic fat globules. She was subsequently referred for local radiotherapy.

Results

The radiological features are summarised in Table 2.

SITE

Five of the nine patients had unilateral right orbital mass lesions; three of these patients had involvement of both the upper and lower preseptal soft tissues and in one the mass involved only the upper lid. In the child (case 4) the preseptal soft tissues were not involved by the disease process. Of the four patients with bilateral orbital involvement, the disease process was confined to the upper lids in two of the patients.

PROPTOSIS AND GLOBE DISPLACEMENT

Seven of the nine patients had radiological proptosis and of these four patients had associated downward displacement of the globe. In the remaining two patients the position of the globe in the affected eye was normal.

LESION CHARACTERISTICS

In all nine patients the soft tissue mass appeared rather infiltrative with poorly defined margins in places and in six patients had a somewhat heterogeneous appearance consisting of both fat and soft tissue elements. In seven patients the mass involved the preseptal soft tissues predominantly but in all cases there was some degree of extension and moulding around the globe. Two patients had single small high density flecks within the lesion visible on CT suggesting calcification. In four of five patients who had contrast enhanced studies the enhancement pattern of the masses was somewhat heterogeneous and in the other patient fairly uniform.

INVOLVEMENT OF LOCAL STRUCTURES

Optic nerve

Encasement of the optic nerve superiorly within the orbit was only seen in one patient (case 4); in this patient the mass did not involve the preseptal soft tissues as in the other eight
Figure 7. Unenhanced computed tomogram showing a large ovoid soft tissue mass posterolaterally within the orbit (A), which abuts the globe superiorly (B). Some sclerosis of the lateral orbital margin is seen (arrow) in (B).

Figure 8. Six months later the mass has increased in size, appears more heterogeneous in texture, and there is now definite bony destruction and intracranial extension.

Table 2. Radiological features on CT (and MRI in case 2) of nine patients with orbital xanthogranulomas

<table>
<thead>
<tr>
<th>Case number</th>
<th>Proptosis</th>
<th>Globe displacement</th>
<th>Mass characteristics</th>
<th>Optic nerve</th>
<th>Extracocular muscles</th>
<th>Retrobulbar fat</th>
<th>Lacrimal glands</th>
<th>Bone involvement</th>
<th>Intracranial extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>present</td>
<td>downward</td>
<td>partially enhancing infiltrative fat and soft tissue mass in right upper and lower lid—extension around globe. Later left lower lid swelling enhancing soft tissue mass and fat in right upper lid with extension posterior to globe. Left lower lid swelling enhancing soft tissue mass and fat in right upper lid with extension posterior to globe.</td>
<td>normal</td>
<td>right all enlarged</td>
<td>increased density</td>
<td>normal</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>present</td>
<td>downward</td>
<td>right upper/lower preseptal soft tissue and fatty mass—posterior extension around globe</td>
<td>normal</td>
<td>enlarged right superior rectus</td>
<td>normal</td>
<td>normal</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>present</td>
<td>none</td>
<td>right upper/lower preseptal soft tissue and fatty mass—posterior extension around globe</td>
<td>normal</td>
<td>enlarged right lateral rectus</td>
<td>normal</td>
<td>normal</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>present</td>
<td>downward</td>
<td>heterogeneous density right soft tissue mass with single high density fleck encased superiorly infiltration of right superior rectus</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>5</td>
<td>absent</td>
<td>none</td>
<td>bilateral soft tissue and increased fat in upper lids—extension into superior orbit enlarged superior recti and left lateral and medial recti</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>absent</td>
<td>none</td>
<td>infiltrative right soft tissue mass</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>present</td>
<td>downward</td>
<td>infiltrative right soft tissue mass</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>right enlarged</td>
<td>none</td>
</tr>
<tr>
<td>8</td>
<td>present</td>
<td>none</td>
<td>right upper/lower preseptal soft tissue mass and prolapse of retrobulbar fat</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>right enlarged</td>
<td>none</td>
</tr>
<tr>
<td>9</td>
<td>absent</td>
<td>none</td>
<td>right upper/lower preseptal soft tissue thickening</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>right enlarged</td>
<td>none</td>
</tr>
</tbody>
</table>
patients, but was predominantly extracranial situated posterolaterally within the orbit.

Extraocular muscles
All nine patients had enlargement of local extraocular muscles; this ranged from various degrees of muscle thickening and enlargement in seven patients to definite infiltration in two patients.

Lacrimal glands
Three of five patients with unilateral orbital diseases had ipsilateral lacrimal gland enlargement; in one of these patients (case 9) the lacrimal gland was primarily involved by the disease process and there was only mild associated thickening of the upper and lower preseptal soft tissues. Of the four patients with bilateral orbital disease, one patient had bilateral lacrimal gland enlargement, one unilateral enlargement, and in the other two both lacrimal glands were normal.

Retrobulbar fat
Mild increase in the attenuation of the retrobulbar fat was seen in two patients suggesting either local infiltration or hypervascularity.

Bone involvement/intracranial extension
Local bone destruction by the orbital mass was only seen in one patient (case 4) who also had evidence of intracranial extension.

None of the other patients had evidence of bony scalloping or pressure resorption.

Discussion
Periorbital xanthogranulomas can be divided into three clinical categories: adult xanthogranulomas some with features of necrobiosis, Erdheim-Chester disease, and juvenile xanthogranulomas.

Periorbital xanthogranulomas are bilateral yellow-orange nodular or plaque-like lesions which, in contrast with periorbital xanthelasma, are often deeper, indurated, and locally invasive, with a tendency to ulceration. Since xanthelasma may have a similar histological appearance in superficial biopsies, histological misdiagnosis is a risk. Xanthogranuloma may be associated with a wide spectrum of haematological abnormalities including paraproteinemia, plasmacytosis, leucopenia, cryoglobulinaemia, or complement deficiency. There is also a recognised association between malignancies such as multiple myeloma and non-Hodgkin’s lymphoma in particular with the necrobiotic form, and it is thus important to recognise this clinical entity. Other described associations include hepatosplenomegaly, mildly raised serum lipid levels, and diabetes mellitus; two of our patients had hypercholesterolaemia and one diet controlled diabetes mellitus (Table 1).

The pathogenesis of orbital xanthogranuloma is not entirely clear, although an immunologically mediated mechanism has been suggested. This is supported by the wide spectrum of immunological abnormalities described in this condition and which in our patients included leucocytosis, eosinophilia, low C4 complement factor, raised immunoglobulins, and elevated rheumatoid factor. The majority (seven out of nine) of our patients also suffered from other systemic diseases thought to have an underlying immune basis such as psoriasis, asthma, thyroid disease, and lymphoid hyperplasia (Table 1).

Two of the four patients with asthma had evidence of necrobiosis histologically; although the association of asthma and orbital xanthogranuloma is well recognised it has only been very rarely described in association with the necrobiotic form of this disease entity. Bullock and colleagues suggested that abnormal serum immunoglobulins present in patients with orbital xanthogranulomas react with tissue lipids and the immune complexes formed elicit a foreign body giant cell reaction. The natural history of untreated lesions is one of progression and the response to therapy—surgical debulking, radiotherapy, steroids, and cytotoxic agents (such as chlorambucil, nitrogen mustard, cyclophosphamide, and melphalan)—is variable.

Orbital xanthogranulomas show characteristic histological features, with a prominent histiocytoid infiltrate resulting in granuloma formation. Foreign body and Touton giant cells are present, the latter having multiple nuclei arranged around central eosinophilic cytoplasm and separated by a rim of foamy translucent cytoplasm from the cell membrane; in the necrobiotic form there may be areas of hyaline necrobiosis characterised by collagen degeneration. Lymphoid nodules, cholesterol clefts, and foci of plasma cells may also be observed. The lipid filled histiocytes give the yellow coloration of the lesions, which can be appreciated clinically and at surgery.

Erdheim-Chester disease is the association of adult onset xanthogranulomas with systemic disease, which characteristically presents as diffuse sclerosis of the diaphysis and metaphysis of long bones. Other reported associations include hepatic adenomas, nephromegaly, hepatosplenomegaly, and xanthogranulomatous infiltration of omentum, mesentery, and lungs. Although ocular involvement is rare in Erdheim-Chester disease, patients with xanthogranuloma lesions on the eyelids and prophotosis secondary to retrobulbar soft tissue masses have been described. The histopathological features of this condition are similar to those of necrobiotic xanthogranuloma.

The adult patients described in this paper had a final histological diagnosis of orbital xanthogranuloma, two with features of necrobiosis histologically. Most of the tissue showed features similar to xanthelasma, but the depth of the lesion or involvement of orbital structures, together with the large size of the infiltrate were distinguishing features. None had systemic evidence of Erdheim-Chester disease. There was CT evidence of proptosis, abnormal soft tissue, and increased fat within the preseptal soft tissues on the affected side in the majority of patients, with bilateral disease in four patients (cases 1, 2, 5, and 6). The infiltrative nature of the xanthogranuloma was
demonstrated radiologically as posterior extension around the globe in all cases (most marked in case 1), involvement of the extracocular muscles, and, in five cases, lacrimal glands. In fact, involvement of the lacrimal glands can occur without the typical skin lesions seen in our patients. The progressive nature and variable response of this condition to treatment modalities is shown on sequential CT in case 1. None of the adult patients had local bony destruction or intracranial extension. The MRI in case 2 confirmed the CT findings and did not add any further useful information.

Juvenile xanthogranuloma is primarily a cutaneous disorder occurring in infants and young children, but occasionally in adults, which may have orbital or ocular involvement. This usually presents as xanthogranulomatous infiltration of the iris, which can result in hyphaema and glaucoma, but less commonly can involve the eyelid, orbit, and optic nerve. Most patients with orbital involvement do not have associated typical cutaneous lesions and present with proptosis or a mass. The irregular soft tissues were not a feature with the adult patients, the preseptal findings and did not add any further useful information.

The main role for imaging in this condition is to show the extent of the lesion and any involvement or displacement of local structures, which is a prerequisite for surgery or when planning radiotherapy. The extent of bony involvement or intracranial extension, a feature of the juvenile but not the adult form of this condition, can be assessed.

In conclusion, the diagnosis and management of orbital xanthogranuloma requires a combined approach: it is important that ophthalmologists, pathologists, and radiologists discuss potential cases since any one discipline is often unable to arrive at the correct diagnosis. Adult patients should be referred to a haematologist for assessment, particularly if necrobiosis is evident histologically.

References:

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