BSD Workshop: Case 25 RAC5556

Clinical Image removed from Presentation
• F49
• Migraine
• Single miscarriage
• 1 year history gradually progressive skin discoloration

Clinical Image removed from Presentation
Initial investigations (2008)

- IgG anticardiolipin antibodies (IgG aCL): 190.8 GPL kU/L

→ 75mg aspirin od commenced
2010

- Odd sensory disorder right arm
- Nerve conduction studies:
  - Non-specific sensori-motor neuropathy
- Ongoing sensory disorder in hands and leg cramps
Investigations: June 2011

- Atypical p-ANCA detected and Myeloperoxidase (MPO) < 1 kU/L → identical results in September 2011
- IgG aCL: 2.7 GPL kU/L
In July 2011, she developed crops of necrotic papules within areas of livedo racemosa on her ankles.
Differential Diagnosis for BSD Workshop

- Polyarteritis nodosa
- Livedoid vasculopathy
- Microscopic polyarteritis
- Chrug Strauss syndrome
- Cholesterol embolism
Histology Report:
Lymphocytic true vasculitis including muscular vessels in the subcutis with widespread thrombosis of superficial vessels.

Appearances in keeping with a systemic vasculitis, such as polyarteritis nodosa. In view of the widespread thrombotic element, suggest ruling out additional coagulopathy including cryoglobulins.

Necrotic plaques resolved with a course of high dose prednisolone
Investigations: February 2012

- ANCA negative
- MPO: 
  < 0.2 kIU/L
- IgG aCL: 
  0.8 GPL kU/L
Other Normal investigations: 2008 - 12

- FBC
- U&E
- LFT
- ESR
- CRP

- Vasculitis screen including:
  - Proteinase 3 antigen
  - Lupus anticoagulant antibody
  - ß-2-glycoprotein-1 antibody
  - Clotting
  - Cryoglobulin & cryofibrinogen
  - Hepatitis B serology
Favoured Clinicopathological Diagnosis

Cutaneous polyarteritis nodosa (c-PAN)
Current daily treatment

- 5mg prednisolone (on reducing dose since Aug ‘11): No further ulcers or chilblains
- 300mg aspirin (dose increased from 75mg in Aug ‘11) – but livedo racemosa progressing
- 50mg losartan (started in April ‘12)
- 45mg amitriptyline & 10mg rizatriptan
- Omeprazole & Calcichew
Livedo racemosa

- First introduced by Ehrmann in 1907\(^1\)
- Originates from the Latin word *racemus* (bunch / cluster of grapes)
- No effective treatment for livedo racemosa & may extend despite antiplatelets or anticoagulants

Biopsy of livedo racemosa\textsuperscript{2,3}

- Biopsy uninvolved skin at the centre of a livedo racemosa area and affected area
- Obtain deep, adequate size biopsies (1-2cm)
- More than 1 biopsy:
  - Sensitivity of biopsy increases from 27% (1 biopsy) to 80% (3 biopsies)
- Obtain serial sections of the biopsies

## Livedo racemosa vs livedo reticularis

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Livedo racemosa</th>
<th>Livedo reticularis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>More generalised</td>
<td>Location: Limbs</td>
</tr>
<tr>
<td>Shape</td>
<td>Irregular, broken circular segments</td>
<td>Shape: Regular, enclosed circular segments</td>
</tr>
</tbody>
</table>

| Physiology | Reduced blood flow and oxygen tension at the peripheries of the skin segments |

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Always pathological</th>
<th>Physiologic livedo reticularis (cutis marmorata)</th>
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<tbody>
<tr>
<td></td>
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<td>Primary livedo reticularis</td>
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<td>Idiopathic livedo reticularis</td>
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<td>Amantadine-induced livedo reticularis⁶</td>
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</tbody>
</table>

Diseases associated with livedo racemosa

- Sneddon’s syndrome
- Antiphospholipid syndrome
- Systemic lupus +/- APS
- Polyarteritis nodosa
- Livedoid vasculopathy
- Cholesterol embolisation

Rare Associations
- Polycythaemia ruba vera
- Essential thrombocytaemia
- DIC
- Thromboangiitis obliterans
- Cryofibrogenemia
- Grave’s hyperthyroidism
- Calciphylaxis
- Hyperoxaluria

Sneddon’s syndrome

- Diagnostic hallmark:
  Generalised livedo racemosa and ischaemic stroke
- 1st described by Champion and Rook in 1960
- 1st characterised as a separate and distinct disease process by Sneddon in 1965

Cutaneous polyarteritis nodosa (c-PAN)\textsuperscript{9,10}

- Rare form of vasculitis involving medium sized arteries
- Aetiology unknown
- Chronic condition with relapses and remission
- Good prognosis

Associations with c-PAN

- Common associations:
  - Group A β haemolytic streptococcal infection
  - Hepatitis B infection
  - Inflammatory bowel disease
  - Extended course of minocycline

- Rarer associations:
  - Hepatitis C infection
  - Parvovirus B-19 infection
  - Mycobacterium tuberculosis infection

Clinical features of c-PAN\textsuperscript{9,10}

- Cutaneous manifestations:
  - Tender subcutaneous nodules
  - Livedo racemosa
  - Tender indurated plaques
  - Necrosis
  - Punched-out ulcers
  - Purpura

- Extra-cutaneous manifestations:
  - Fever
  - Myalgia
  - Arthralgia
  - Neuropathy
  - Paraesthesia


Laboratory abnormalities in c-PAN\textsuperscript{9}

- Frequently:
  - Mild anaemia
  - Moderate leukocytosis
  - Raised ESR
  - Anti-phosphatidylserine-prothrombin complex antibody
    \((\text{IgM} >> \text{IgG})^{11}\)

- Rare reported cases:
  - p-ANCA\textsuperscript{12}
  - Lupus anticoagulant antibody\textsuperscript{11}
  - Anticardiolipin antibody \((\text{IgG}^{11,12} > \text{IgM})\)

\textsuperscript{12} Pereira BAF et al. Cutaneous polyarteritis nodosa in a child with positive antiphospholipid and p-PANCA. \textit{Scand J Rheumatol} 1995;24:386-8
Treatment of c-PAN\textsuperscript{9,10}

- NSAIDS
- Colchicine
- Aspirin
- Steroids
- Steroid sparing agents
- Dapsone
- IV Ig

- Perilesional injections of granulocyte-macrophage colony-stimulating factor\textsuperscript{13}

RSM: Summary

- Case of generalised livedo acemosa
- Features entirely in keeping with c-PAN

BUT.... Dr R disagreed
Dear X and other colleagues involved in this lady`s case

This is a case of **antiphospholipid-syndrome** and as such no vasculitis, but a coagulopathy. Clinically, livedo (in this case racemosa) is characteristic of a coagulopathy and on the lower legs there is in addition also livedo vasculopathy (by others in my experience wrongly called livedo vasculitis).

As I showed in my presentation in Oxford this disease shows in stage II beside presence of fibrin thrombi (which would be stage I when present alone) plentiful lymphocytes accentuated around a superficial defect (as shown here in your series of histologies), but also involving deeper and larger vessels. This is yet an expected finding of reorganisation of stage I and will end as restitutio ad integrum or scar formation, atrophy blanche clinically and fibrosis, stage III livedo vasculopathy histologically.
Laboratory work up (it is typical that some coagulopathic parameters may become positive and negative in due course of disease showing undulation/roller-coaster of coagulation cascade) and previous history (abortion, misscarriage) excellently fit APS. The question is if patient will develop lupus erythemathodes or another collagenosis/systemic disease in due course which is well established in the literature. Previously, such cases would have been considered in the field of Sneddon syndrome, but this was before the respective laboratory parameters were worked out. And these laboratory parameters nicely parallel the ulcers, i.e. in livedo racemosa with livedo vasculopathy one has a much greater chance to find a causative coagulation factor than without ulcers.

Many thanks for sharing this case with me

Best greetings, from Innsbruck, Bernhard (zelger)
Just as an attachment / addition to my previous email. Classic PN (panarteriitis nodosa) characteristically affects arteries (or arterioles) at the border dermis-subcutis only, very rarely there is superimposed livedo vasculopathy which might then be difficult to differentiate histologically.

Clinically, in classic PN nodules are present beside livedo racemosa which is then also more starry sky-like (i.e. inflammatory) and shows in addition severe arthropathy of ankle region the latter of which by the way is mostly the earliest clinical finding.

Microscopic PN is (completely) different. It accentuates postcapillary venules and may also involve larger vessels. In your case accentuation is on capillaries.

Best greetings

Bernhard
Learning Points

• Always be prepared to re-assess a diagnosis
• Don’t be afraid to get it wrong
• Don’t be afraid to ask for help!

Thank You