Case presentation

Polyneuropathy and a paraprotein

small clone – big problem

ESIM Winterschool – jan 2013

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Case history:
60 year old man with pain and swelling of the feet

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- 2011:
  Pain in both feet, accompanied by swelling of the feet/ankles.
  Blue-ish discoloration of the hands.

- Evaluated by several specialists in “St. Elsewhere”:
  - rheumatologist: diagnosis “arthralgia of unknown origin”
  - vascular surgeon: no diagnosis
  - neurologist: no diagnosis

- 2012:
  Facial rash. Biopsy: “lupus-like skin reaction”.
  Receives topical corticosteroid.
  Again referral to rheumatologist. Conclusion: no systemic LE.

Case history:
60 year old man with pain and swelling of the feet

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- 2012:

  Progressive difficulty walking and getting up stairs (leg weakness).
  Reduced sensation in feet.

- EMG:

  Multifocal demyelinating disease causing sensory and motor neuropathy

- Protein electrophoresis: monoclonal band

- Referred to hematologist for further analysis

Paraprotein & polyneuropathy
- a differential diagnosis

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Paraprotein & polyneuropathy - a differential diagnosis

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- Multiple Myeloma
- MGUS

- Specific syndromes:
  - Amyloidosis
  - POEMS syndrome
  - Waldenstrom's disease
  - IgM related polyneuropathy, e.g. anti-MAG associated
  - CANOMED syndrome
    Chronic Ataxic Neuropathy
    Ophthalmoplegia
    M-protein (IgM)
    cold agglutinins
    Cisialosyl (anti-ganglioside anti-GD1b and anti-GQ1b) antibodies

Paraprotein & polyneuropathy - a differential diagnosis

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- Multiple Myeloma
- MGUS

- Specific syndromes:
  - Amyloidosis
  - POEMS syndrome
  - Waldenstrom's disease
  - IgM related polyneuropathy, e.g. anti-MAG associated
  - CANOMED syndrome

In this patient: **IgA-lambda** paraprotein *small non quantifiable band* with normal kappa / lambda free light chains

POEMS syndrome – diagnostic clinical criteria

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Mandatory criteria *(both required)*

Polyneuropathy

Monoclonal plasmaproliferative disorder

Major diagnostic criteria *(1 required)*

Vascular endothelial growth factor (VEGF) level elevation
Sclerotic bone lesions
Castleman's disease

Minor diagnostic criteria *(1 required)*

Organomegaly
Extravascular volume overload
Endocrinopathy
Skin changes
Papilledema
Thrombocytosis / polycythemia

Other symptoms

Clubbing, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diathesis, diarrhea, low vitamin B12 levels

Physical examination:
“lupus like skin eruption”

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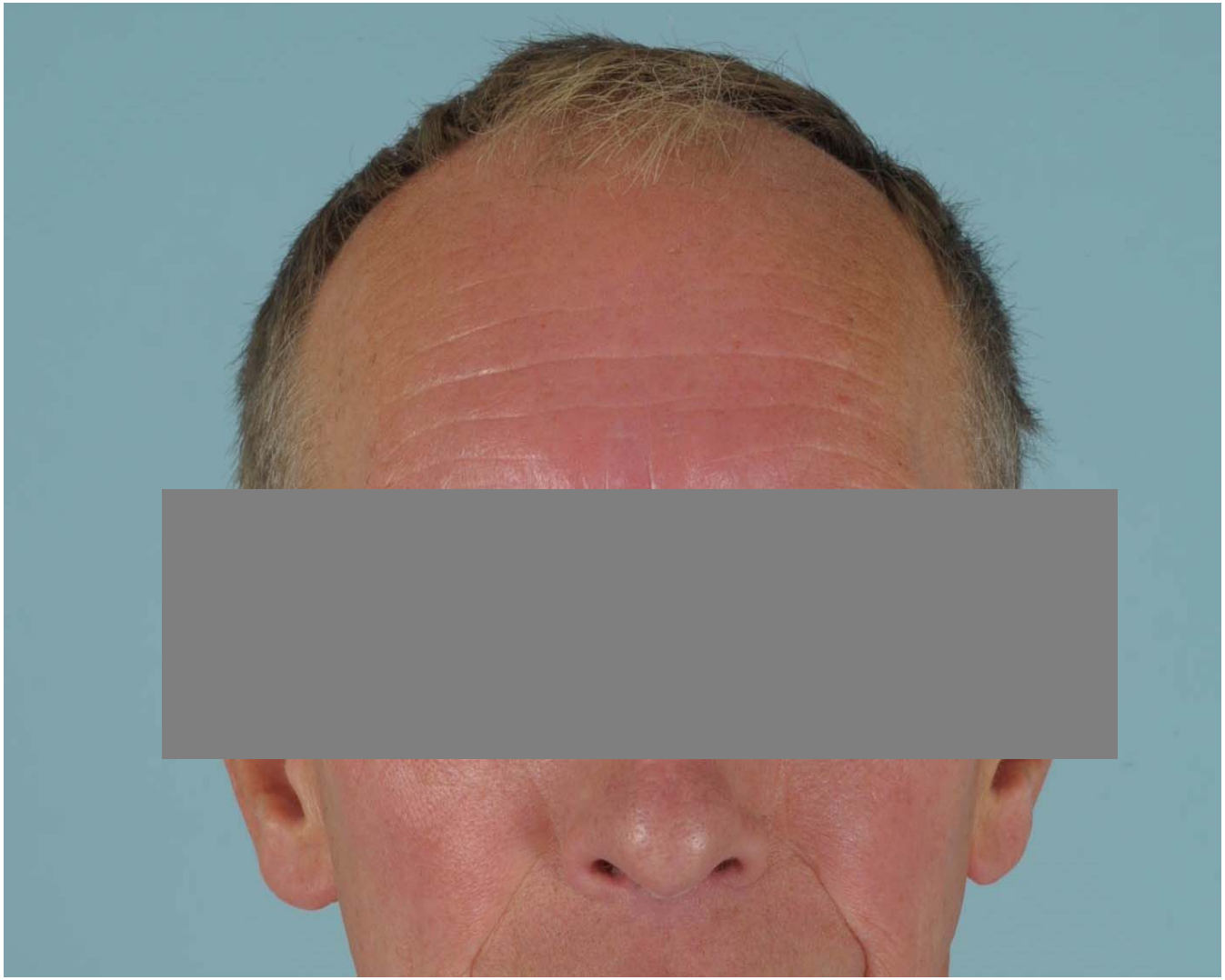

Physical examination: acrocyanosis

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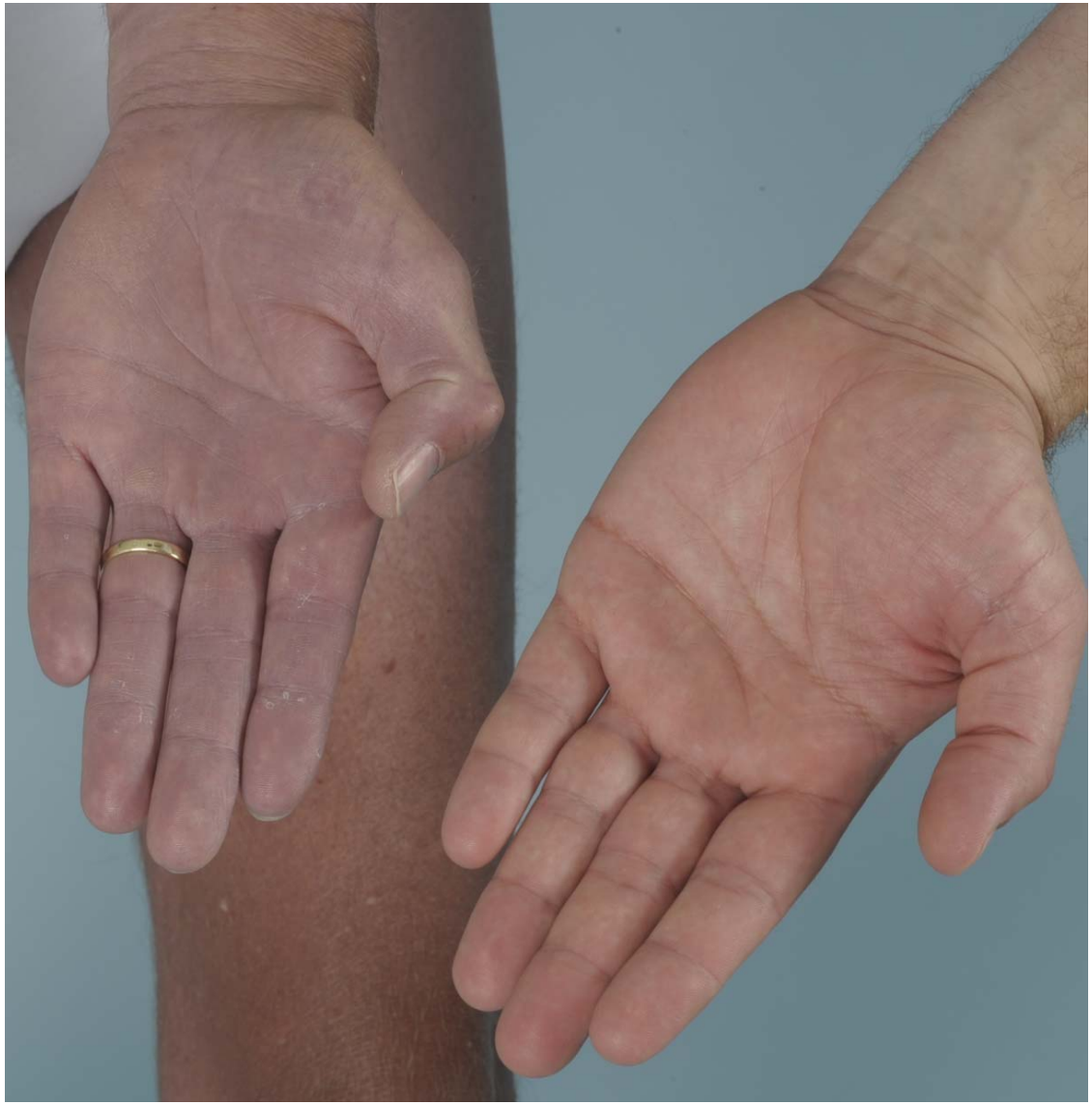

Physical examination: hyperpigmentation & hypertrichosis

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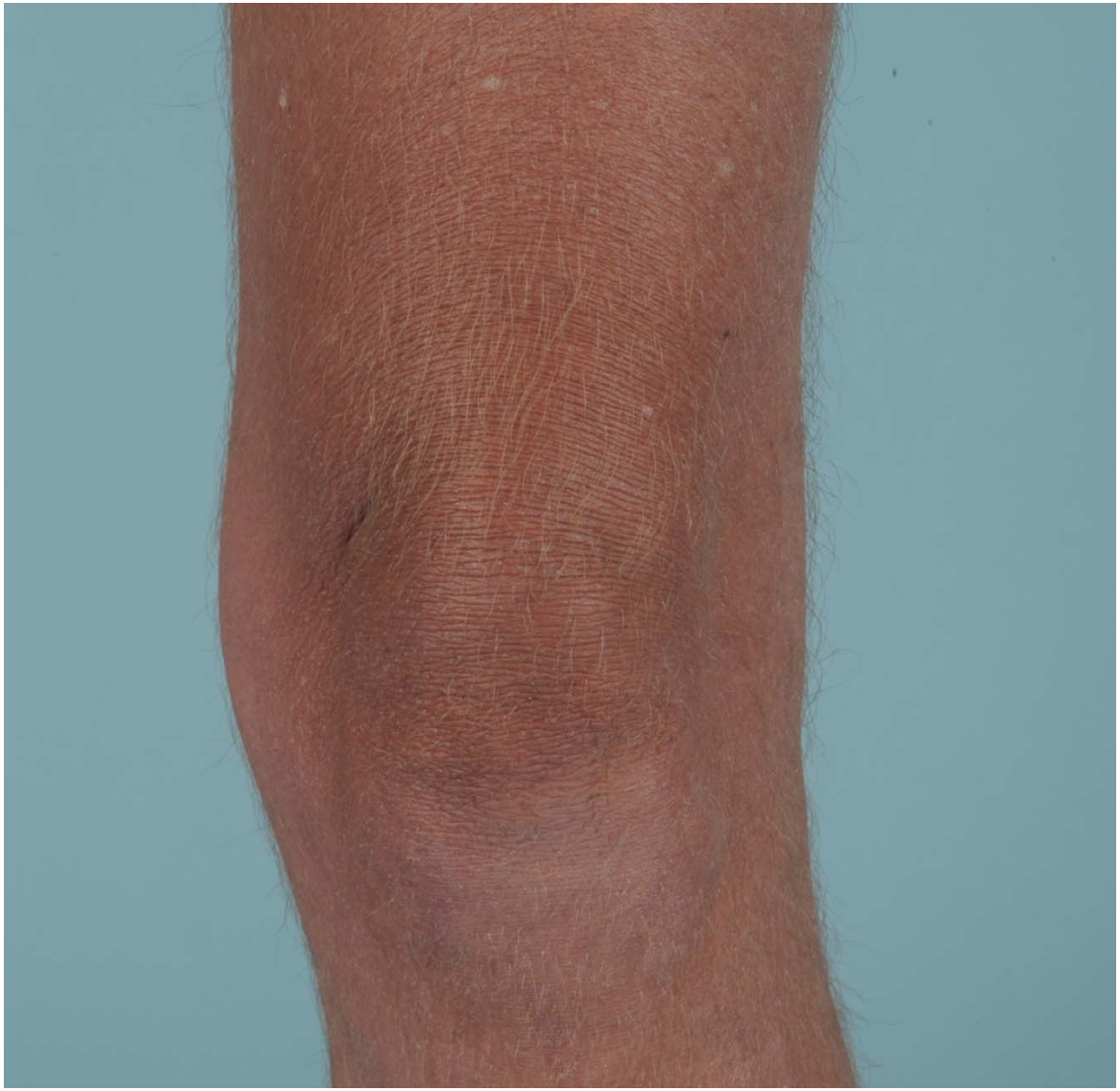

Physical examination: Peripheral pitting edema

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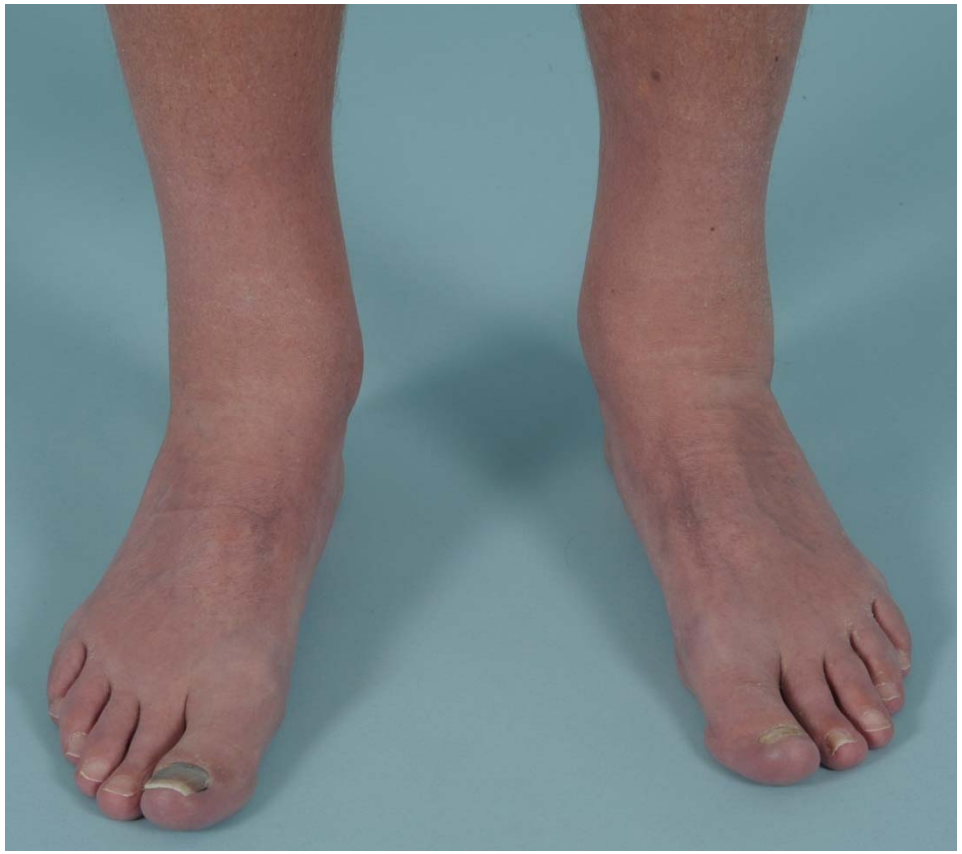

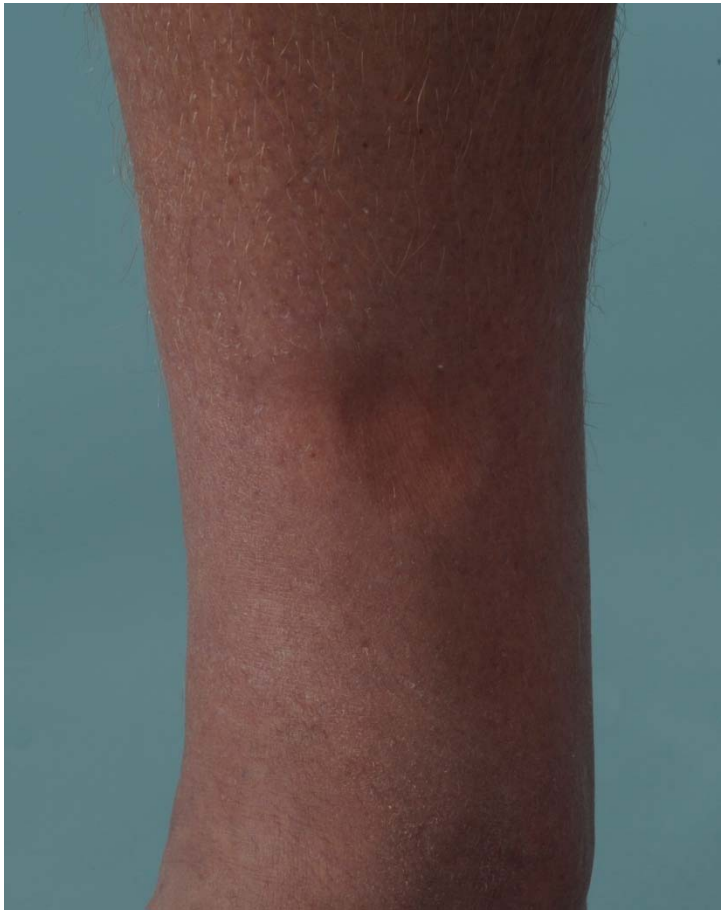

Laboratory testing

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- IgA-lambda paraprotein – detectable, but non-quantifiable
  Free light chain levels and - ratio normal
  Beta-2-microglobulin increased (4.2 mg/l)
- Marginal thrombocytosis (434 $x10^9$/l) with otherwise normal CBC
- Routine chemistry and electrolytes all within normal limits
- Endocrinological testing:
  - Hypogonadism with testosterone level of 5.3 nmol/l (ref 7.0-31)
  - Adrenal insufficiency:
    - Morning cortisol level 0.27 µmol/l
    - ACTH-test: maximum peak 0.39 µmol/l (ref >0.50 µmol/l)
- VEGF: 17156 pg/ml (ref 10 – 150)
- Vitamin B12: 81 pmol/l (ref 130-700)

CT-whole body: multiple sclerotic bone lesions + (modest) splenomegaly

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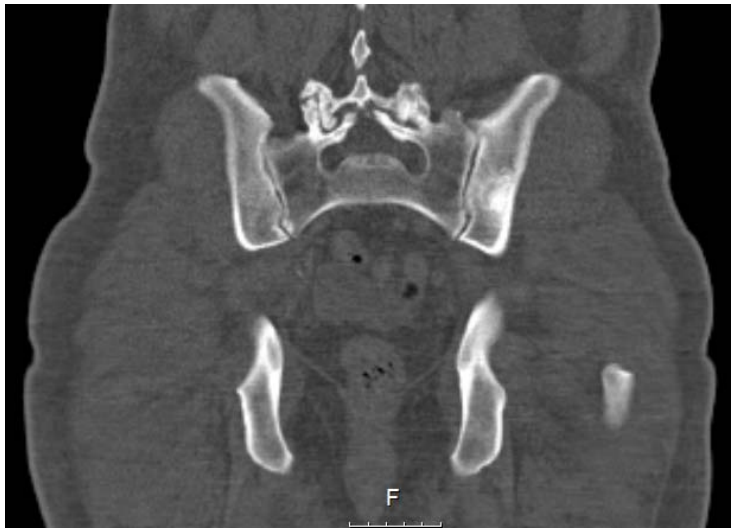

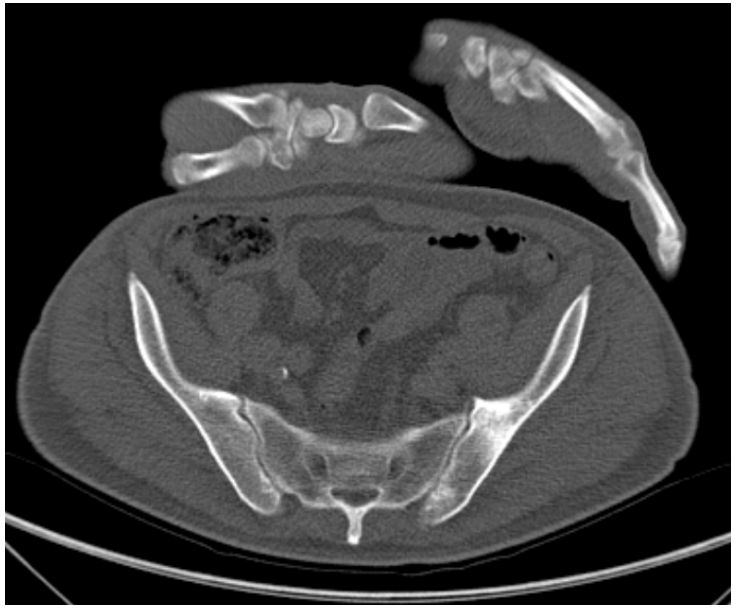

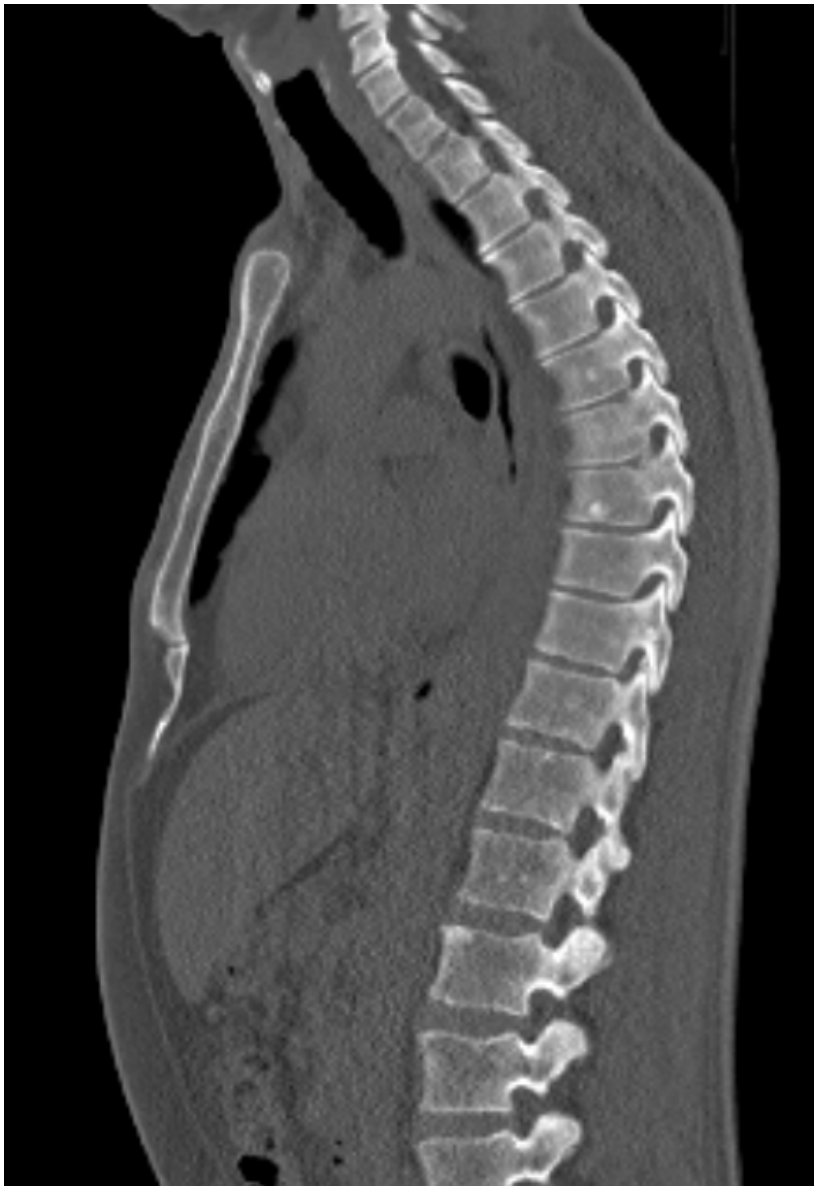

Ophthalmologist: bilateral papilledema (asymptomatic !)

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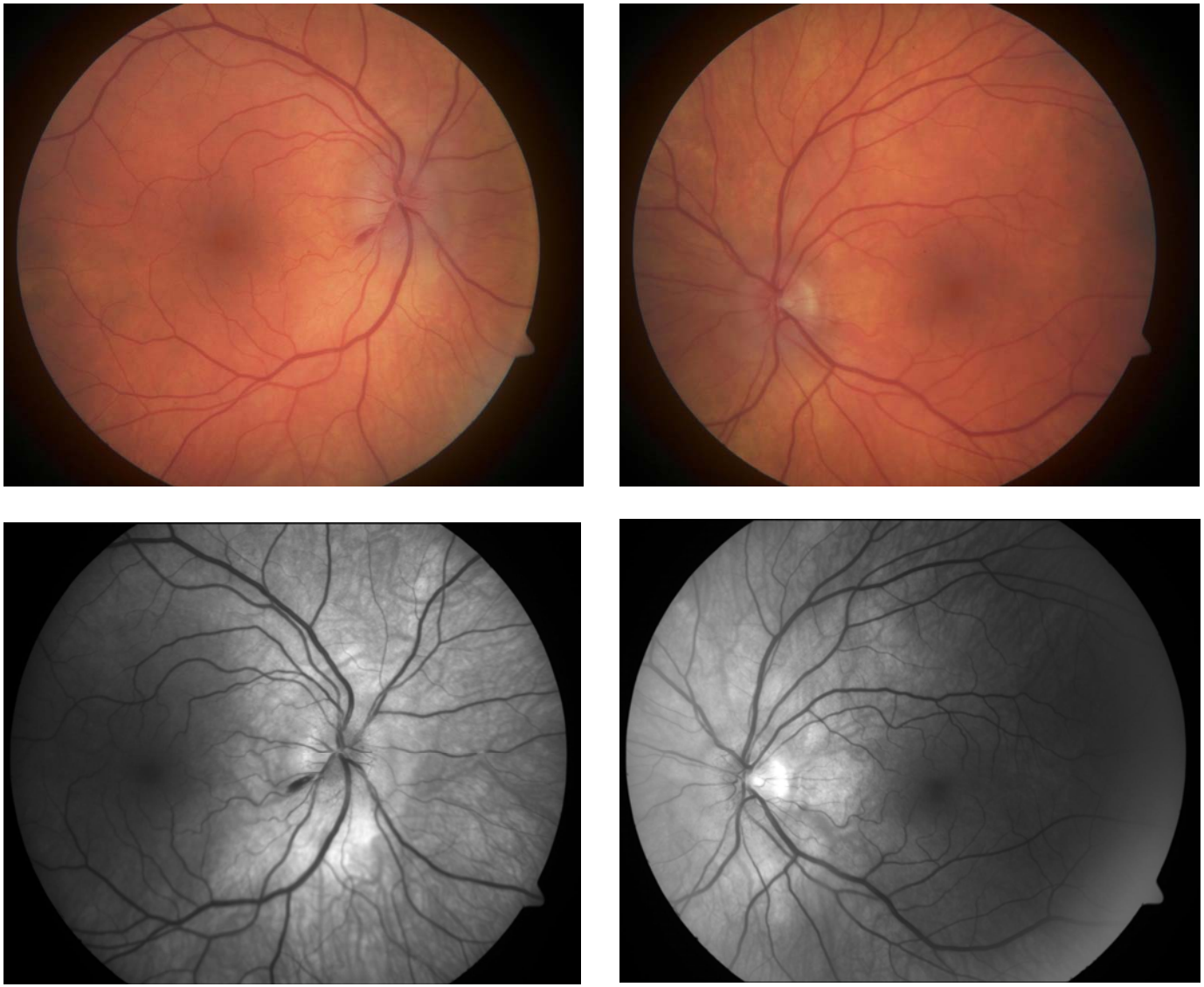

Making the diagnosis:
Some subtle, but all there !

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Mandatory criteria *(both required)*

Polyneuropathy	+
Monoclonal plasmaproliferative disorder	+

Major diagnostic criteria *(1 required)*

Vascular endothelial growth factor (VEGF) level elevation	+
Sclerotic bone lesions	+
Castleman's disease	-

Minor diagnostic criteria *(1 required)*

Organomegaly	+
Extravascular volume overload	+
Endocrinopathy	+
Skin changes	+
Papilledema	+
Thrombocytosis / polycythemia	+

Other symptoms

Clubbing, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diathesis, diarrhea, low vitamin B12 levels	+

To fight the clone, find it we must…

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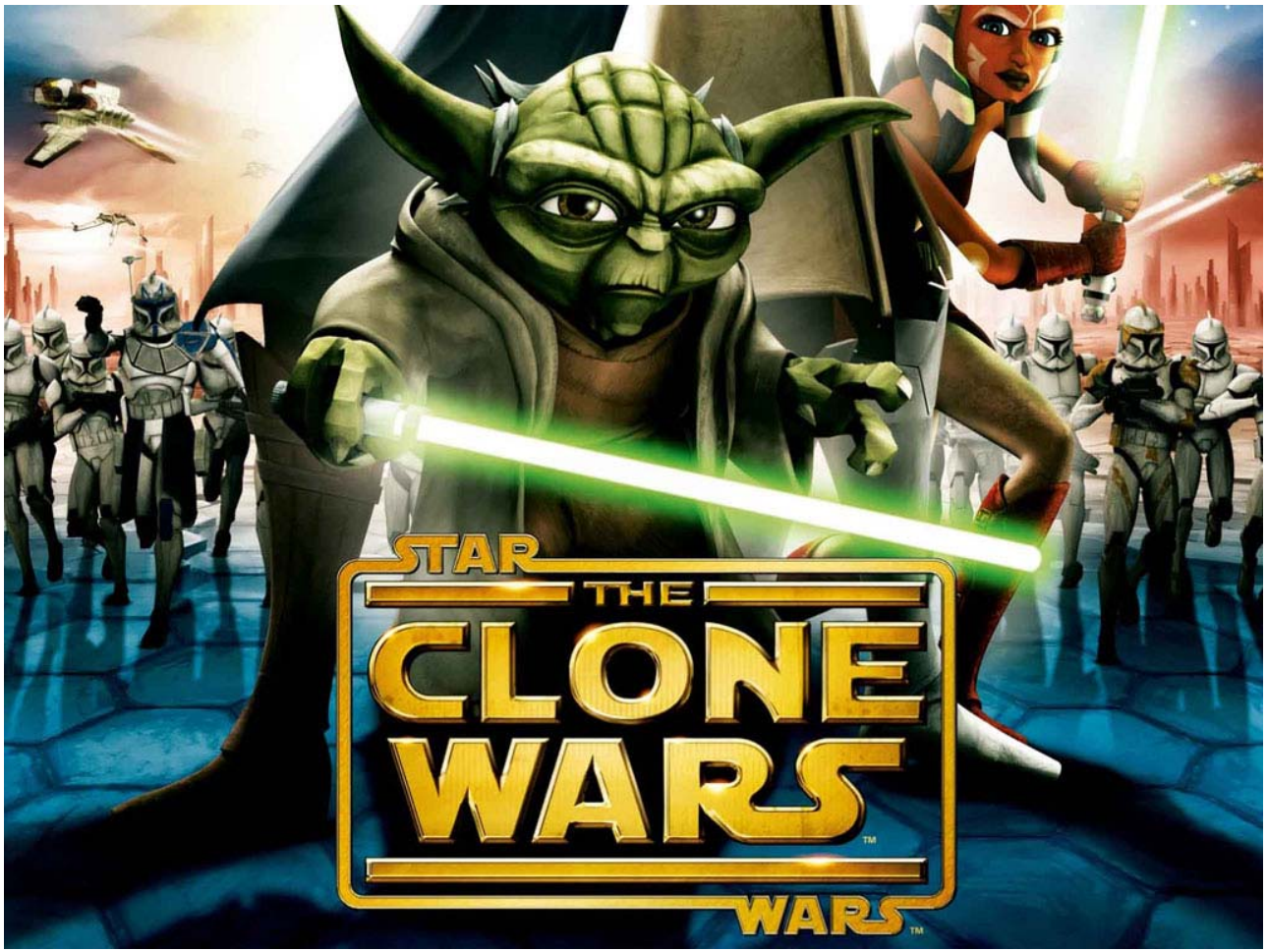

Bone marrow investigation: normal !

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Cytomorphology:	1 % plasma cells (normal)
Immunophenotyping (flow cytometry):	0.09% plasma cells all polyclonal
Histology:	5% plasma cells polyclonal

Peripheral blood immunophenotyping

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0,004% of nucleated cells are circulating plasma cells

No kappa/lambda restriction: polyclonal !

Osteosclerotic lesions: FDG-PET-negative ! (in our patient)

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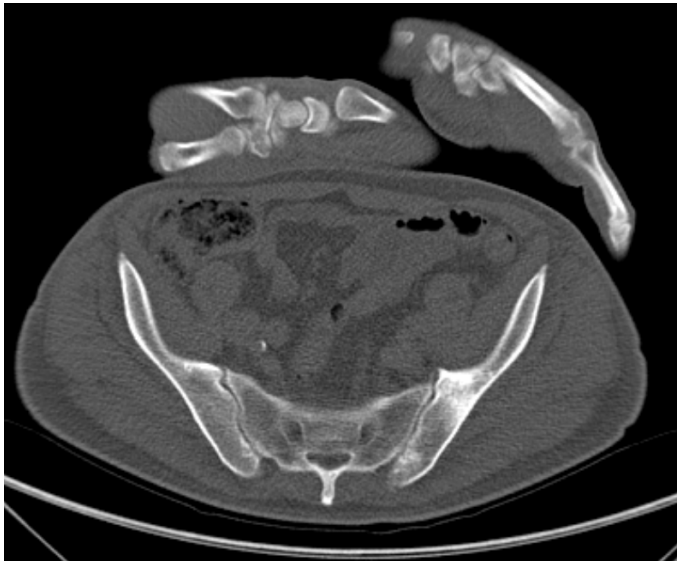

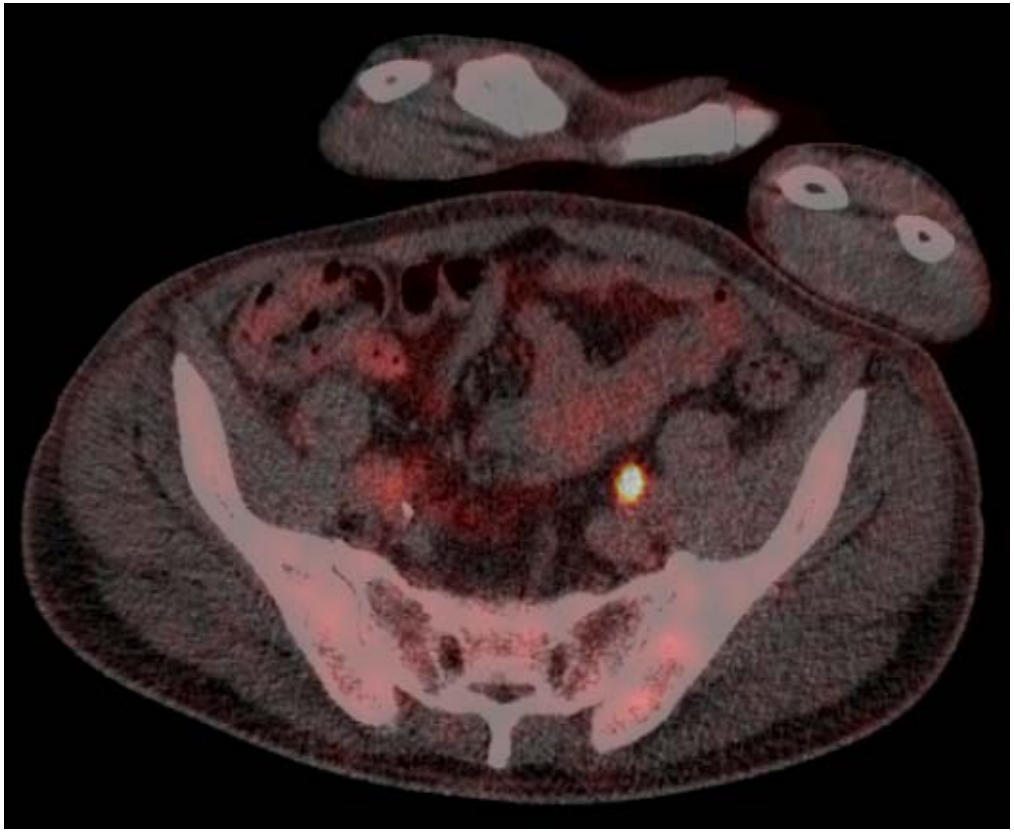

Case – follow-up

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Sep 2012	diagnosis hydrocortisone + testosterone + vitamin B12 supplementation stem cell apheresis after 5 days G-CSF
Oct 2012	high-dose melphalan (2 days 100mg/m2) autologous stem cell transplantation
Nov 2012	hospital admission with neutropenic fever repopulated
Dec 2012	slow recovery – fatigue, poor performance
Jan 2013	improving general health no further progression of polyneuropathy IgA-lambda band no longer detectable

What I learnt from this case

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- Small plasma cell clones can cause major disease

  beware of a small IgA-lambda band
  in a polyneuropathy patient !

- Knowing what to look for makes you see

Additional slides for discussion

Treatment

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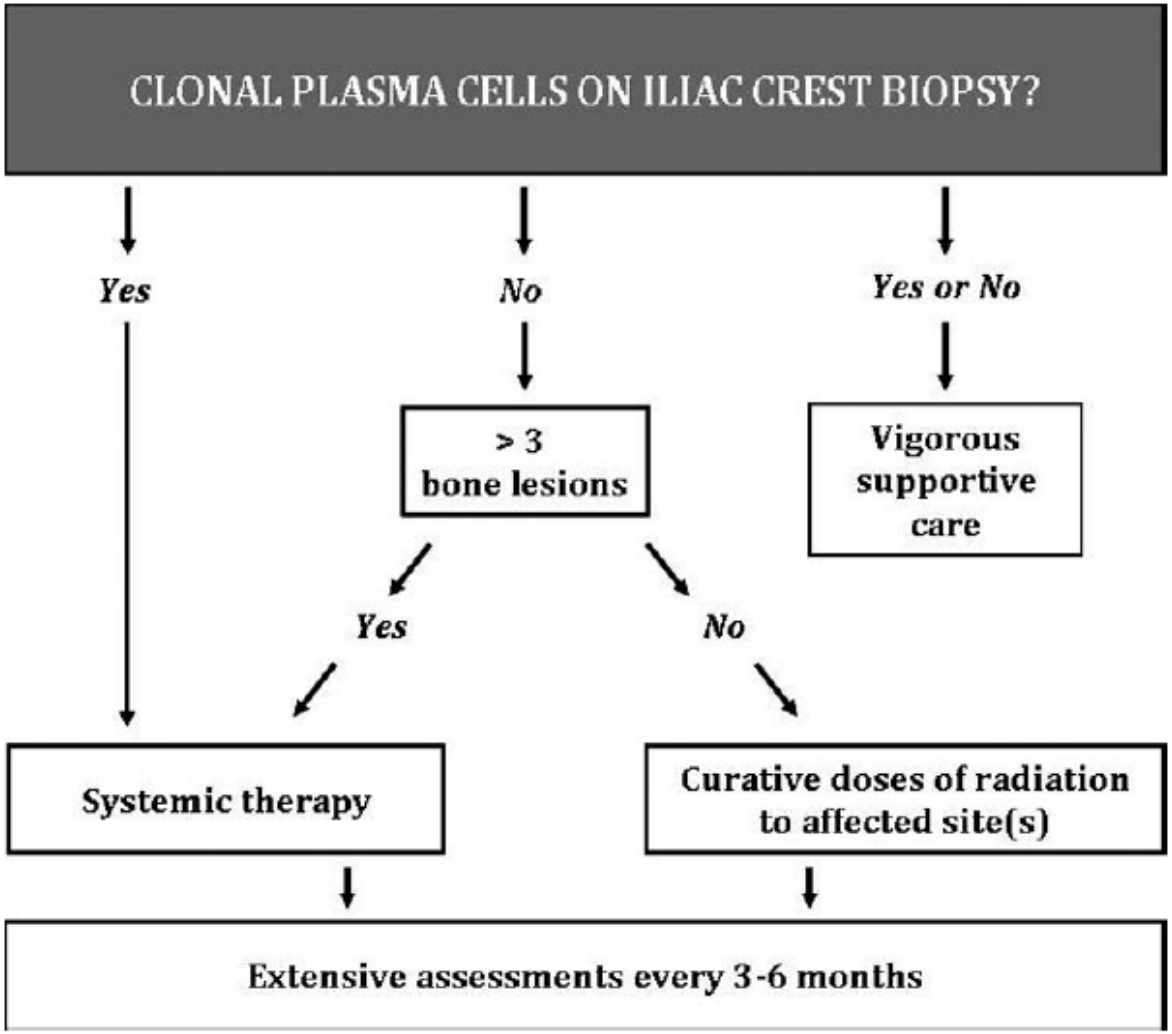

Figure 1. Algorithm for the treatment of POEMS syndrome.

Dispenzieri et al. Blood 2012

Systemic therapy

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1st choice:

high dose melphalan + autologous stem cell transplantation

Alternatives:

- Intermediate dose melphalan
- Melphalan / dexamethasone
- Thalidomide / dexamethasone
- Lenalidomide / dexamethasone (/ cyclophosphamide)
- Bortezomib / dexamethasone

Dispenzieri et al. Blood 2012

POEMS syndrome
“osteosclerotic myeloma”

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“Pathological paraprotein”, nearly always lambda clone.
IgG or (often!) IgA

Exact pathogenesis of the disease is unclear

High circulating levels of cytokines IL-1, IL-6, VEGF, and TNF
Low circulating levels of cytokine TGF-β

VEGF-inhibition alone (bevacizumab) ineffective