was noted with low doses of prednisone, however, in contrast with the dramatic improvement obtained in the original papers. On the other hand, synovial biopsy in our case did not show malignant infiltration. Thus it is reasonable to suggest that the rheumatic manifestations belong to a paraneoplastic syndrome, as has been previously reported with other neoplasms. To our knowledge this is the first description of peripheral synovitis and pitting oedema as an initial manifestation of non-Hodgkin's lymphoma. We would like to emphasise the need to consider the possibility of an underlying malignancy in a patient with these clinical characteristics who is unresponsive to the usual medical treatment.

M R ROLDAN  
Department of Rheumatology  
'Rema Sofia' Hospital  
Cordoba  
Spain

J ROMAN A TORRES  
Department of Rheumatology  
'Rema Sofia' Hospital  
Cordoba  
Spain

Correspondence to: M Rosa Roldan Molina, c/Sanchez de Feria 3, 1º 3, 41003 Cordoba, Spain.


Arthritis and carcinoma

Sir: We read with interest the paper by Chakravarty and Webley describing two cases of asymptomatic renal cell carcinoma causing an acute monarthritis, previously unreported. They suggested that this occurrence is both rare and underreported. In our experience this is not necessarily the case. We have recently seen two patients whose cases illustrate some interesting similarities.

Patient No 1, a 63 year old man presented to our hospital with a five week history of a painful, swollen knee joint and was unable to bear weight. Clinical examination confirmed an acute monarthritis of the knee joint, with a tense effusion, warmth, and tenderness. He had been treated for a large cell solid temporo-orbital tumour by radiotherapy because the lesion was considered inoperable. The knee joint effusion was aspirated to rule out sepsis. Bacteriology was negative, no crystals were found, but adenocarcinoma cells were seen in abundance. He made an excellent functional recovery after palliative irradiation to the knee.

Patient No 2, a 63 year old woman, was referred to the radiotherapy department of the same hospital with metastatic disease for which no primary tumour had been located despite extensive investigation. She had initially presented with a painful knee of one year's duration. Clinical examination showed an acute monarthritis with a moderate effusion. Isolate bone scan disclosed a hot spot in the upper tibia. She had a synovial biopsy and cytological examination of the synovial fluid. The synovial biopsy sample showed evidence of infiltration of adenocarcinomatous cells as did the synovial fluid.

While we agree with the authors that in cases where there is doubt about the cause of a joint effusion, early examination of synovial fluid is important, and may prevent the need for an open or closed bone biopsy, we are of the opinion that the occurrence of malignant joint effusions is not rare but more likely to be underreported.

CIARAN DUNNE  
TIM LILLYDGE  
Poole Hospital  
Longfleet Road  
Poole

Dorset BH15 2BJ  
United Kingdom

Angiostatin converting  
enzyme in rheumatoid arthritis

Sir: Being interested in vascular endothelial cell transdifferentiation,1 I read with interest the instructive articles by Veale et al2 and Goto et al3 about the angiostatin converting enzyme production in rheumatoid arthritis. Although there is no doubt that vascular endothelial cells participate in this process, the role of macrophages remains questionable because the antibodies used for their identification (antiCD14) are not macrophage specific and cross react with vascular endo-
thelial cells.4 Moreover, undifferentiated vascular endothelial cells can transdifferentiate into macrophage-like cells and migrate into the extravascular space. It may be useful to re-evaluate the role of macrophages in rheumatoid arthritis in the light of the new knowledge about the trans-
differentiation of vascular endothelium.5 For example, the mesenchymal transformation cells responsible for joint destruction differentiate into fibroblasts in due course and are not, therefore, inflammatory cells. McCachren considers, however, any collagenase producing cells immunoreactive with Leu-M3 or HAM56 to be macro-
phages.6 Again, these antibodies are not macrophage specific and cross react with vascular endothelial cells.7 Mesenchymal transformation cells contain undifferentiated vascular endothelial cells1 by their character and aggressiveness.7 The facts that antiangiogenesis suppresses arthritis and angiostatin II is an angiogenic factor8 are in excellent keeping with that proposition.

JIRI T BERANEK  
Department of Medicine  
UMC-School of Medicine  
Columbia, Missouri  
USA

3 Goto M, Sasoano M, Fuzisawa M, Okabe T, Nishizawa K. Constitutive production of angiostatin converting enzyme from rheuma-
9 Nickoloff B J, Griffiths C E M. The spangle-
12 Fernandez L A, Twickler J, Mead A. Neovas-

Endothelium damage and von Willebrand factor antigen

Sir: We read with great interest the recent paper by Blann et al on damage to the endothelium in Sjögren's syndrome.1 The authors examined the relation of the auto-

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Correspondence to: Rheumatology, Malalties (the Letters of endothelial increased vWFAg rheumatica reliability artery Temporal peroxidase staining of trates vessels thelium, 21 Rheumatol poralis and specimens from factor Ann Rheum the introduction newv arteritis taken...l..i...j of raised a...of immune...of endothelial these diseases, including Sjögren's syndrome, as a marker of endothelial damage should be reconsidered.

PREBAN ELLING
Department of Internal Medicine
Randers Central Hospital
Randers, Denmark

ANDERS OLSSON
HANNE ELLING
Department of Rheumatology
Viborg County Hospital
Viborg, Denmark

There are no signs of damage to the endothelium, and there have shown that intense production of vWFAg occurs in the many new vessels occurring in the inflammatory infiltrates (figure). The figure also shows the presence of vWFAg as a slight immunoperoxidase staining in endothelium cells. This staining pattern is not different from the pattern seen in normal temporal arteries or in biopsy specimens from patients with polymyalgia rheumatica and normal levels of vWFAg. As similar microvascular abnormalities (the introduction of many new vessels) are present in most of the diseases with increased vWFAg mentioned above, the reliability of raised levels of vWFAg in these diseases, including Sjögren's syndrome, as a marker of endothelial damage should be reconsidered.

AUTHOR'S REPLY: Elling et al propose that raised circulating levels of von Willebrand factor antigen (vWFAg) reflect not endothelial cell damage but production by endothelial cells in newly growing microvasculature, challenging existing dogma. In support of this hypothesis they offer an immunohistochemical photograph from a patient with temporal arthritis taken from a previous publication which examined temporal artery biopsy specimens from patients with arthritis temporalis, polymyalgia rheumatica, and other disease. They found raised serum vWFAg and intense vWFAg staining in new vessels in the lamina elastica only in patients with arthritis temporalis, but offer no mechanism or evidence that these are 'new' vessels. Could it be that the intense staining seen in the elastic lamina is because these endothelial cells are damaged? From the photograph it is difficult to tell if all or part of the intense staining for vWFAg is from intact cells, disrupted cells, or from vWFAg in the general connective tissue stroma.

I am surprised that Elling et al suggest that endothelial damage cannot explain why increased concentrations of vWFAg are present in such varied diseases as proliferative glomerulonephritis, diabetes mellitus, systemic sclerosis, Sjögren's syndrome, and arteritis temporalis, as endothelial damage in these diseases is not a common denominator. Other workers, such as Gömpi et al, have expressed an opposite view, stating that vessel injury is a common feature of scleroderma, glomerulonephritis, diabetes mellitus, Behçet's syndrome, systemic lupus erythematosus, rheumatoid arthritis, and vasculitis in general. There seems to be little disagreement about the presence of raised vWFAg in a large number of conditions, some of which may be characterised by histological evidence of injury to the vasculature. However, the exact mechanism, in many cases, is unclear. Raised vWFAg is common in the acute phase response, but it would be surprising if there was evidence of damaged endothelium in this condition. It may be that in this case endothelial cells are merely 'activated' or 'stimulated' to produce vWFAg in expectation of a more severe insult (i.e. septicaemia) - they may indeed damage the endothelium. Further increases in vWFAg may be the product of increased synthesis by actively growing cells in the capillary beds, the adventitia, or elsewhere. If this were true then one would need to explain why there should be an extra growth of endothelial cells, or upregulated production from a resting cell. Perhaps existing cells are being damaged, possibly through the process of cell death, by a disease process, such as the combined effects of immune complexes and complement in vasculitis or ketocidois in diabetes.

Probably the ultimate proof of injury/damage would be an electron micrograph study of the endothelium in human disease. Such work would need to show a damaged endothelial cell with absent or depleted Willebrand bodies (immunoreactive bodies of vWFAg), ideally with immunocytochemistry for cytoplasmic vWFAg, alongside plasma levels of vWFAg. Another approach may be to look at vWFAg mRNA from in vivo 'damaged' and 'stimulated' endothelial cells - but these data would not provide information about vWFAg in Wielbe-Palade bodies.

Until such data are easily obtained then the hypothesis that raised vWFAg is produced by injured endothelial cells in vivo may never be completely accepted. Yet despite this there remains a wealth of clinical and non-clinical data from many different diseases which all support the hypothesis. Convincing competing hypotheses would need to take account of all these findings.

A D BLANN
Department of Surgery,
University Hospital of South Manchester,
Nell Lane, Didsbury,
Manchester M20 8LF,
United Kingdom


Temporal artery from a patient with arteritis temporalis. Immunoperoxidase and counterstaining with haematoxylin. Von Willebrand factor antigen was localised in endothelial cells of the vessel and in large amounts in new vessels along the lamina elastica.
Endothelium damage and von Willebrand factor antigen.

P Elling, A Olsson and H Elling

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