SIR, A 47-year-old male presented with severe systemic inflammatory response syndrome. A year previously he had noticed a painless swelling in the right fossa poplitea interpreted as Baker’s cyst. Laboratory analysis documented CRP (97 mg/l), ESR (102 mm/h), haemoglobin (98 g/l), slightly elevated liver enzymes and hyperferritinaemia (1236 μg/l), but no autoantibodies. Diagnostic workup comprised bone marrow aspiration, liver biopsy, MRI angiography of the thorax and abdomen, temporal artery biopsy, upper and lower gastrointestinal (GI) endoscopy and biopsies to search for Whipple’s disease, tuberculosis and malignancy. Differential diagnoses such as adult Still’s disease or occult vasculitis were discussed. Short courses of glucocorticoids with 1 mg/kg body weight tapered to 20 mg/day and MTX at 20 mg i.m. weekly were ineffective. Treatment with infliximab at doses of 3.3 mg/kg body weight (in total 200 mg/kg) at weeks 0, 2 and 6 did not elicit any clinical benefit. CRP remained unchanged (150 mg/l).

Three years later he was referred to our outpatient clinic. His condition had worsened: haemoglobin 74 g/l, CRP 156 mg/l, ESR 125 mm/h and polyclonal gammopathy had developed (24.9 g; norm <14.6 g/l). Briefly, the patient showed the classical symptoms and signs of uncontrolled IL-6 production [1]. The cellular source of this cytokine remained enigmatic. The only inflammatory tissue to be identified by imaging methods was the Baker’s cyst, which was judged by experienced radiologists to be an uncomplicated cyst (Fig. 1A).

The patient agreed to off-label therapy using the IL-6-neutralizing monoclonal antibody tocilizumab. He experienced rapid and full remission. Laboratory parameters and his physical condition normalized within a few weeks. Infusions, the first two given at fortnightly intervals, were continued at 4-week intervals at a dosage of 8 mg/kg body weight.

One year later, in a further attempt to identify the source of IL-6, the MRI of the knee was repeated (Fig. 1B). Surprisingly, the morphology of the Baker’s cyst had changed considerably. A substantial part of the heterogeneous tumour was replaced by a large cyst containing homogeneous liquid. We recommended surgical removal, stopped tocilizumab and started to prospectively collect sera for cytokine measurements. Histological analysis documented the unexpected diagnosis of angiomatoid malignant fibrous histiocytoma (aMFH) with production of IL-6 by histiocytoma cells (Fig. 1C–F) [2, 3]. Excision of the neoplasm resulted in complete and lasting remission. Cytokine measurements continuously showed normal concentrations of IL-1, TNF-α and soluble tumour necrosis factor receptor (sTNFR). IL-6 was strongly elevated in synovial fluid and normalized in sera within 8 weeks after surgery.

Many studies have reported elevated systemic levels of proinflammatory cytokines and their antagonists in active autoimmune and inflammatory diseases. Yet clinically it is usually impossible to differentiate between the clinical effects induced by each of the three cytokines. In this case, however, IL-1β, TNF-α and sTNFR-75 remained normal throughout the observation period, while IL-6 was highly elevated until surgery. In addition, blockade of TNF-α using infliximab was completely ineffective with respect to clinical signs as well as control of the acute phase response (e.g. CRP levels), whereas blockade of IL-6 resulted in rapid and lasting complete remission of all pathology findings. In summary the clinical picture and laboratory alterations represent the pleiotropic biological effects of IL-6.

In contrast to its well-characterized effects in inflammation and immunity, the relevance of IL-6 as a mediator of paraneoplastic signs is still unclear. This case is the first to document a remission-inducing effect of IL-6 blockade using tocilizumab in aMFH, thus identifying IL-6 as the key pathogenic factor in the generation of paraneoplasias. In addition to rapid and sustained clinical benefit, a
striking finding was the change in morphology of the neo-
plasm in response to 1 year of IL-6 blockade. The MRI
suggested a decrease in aMFH volume replaced by a
large cyst. This tumour evolution could best be explained
by an autocrine growth effect of IL-6, as described for
example for multiple myeloma and prostate cancer [4].

The effect of IL-6 on differentiation of terminal B cells
into antibody-producing plasma cells was recognized
many years ago [1]. In multiple myelomas, substantial
quantities of IL-6 have been shown to be produced in a
paracrine fashion by surrounding stromal cells [5]. In our
case, immunohistochemistry showed impressive amounts
of IL-6 in aMFH cells, clinically reflected by polyclonal
gammopathy. However, IL-6 was virtually absent in
plasma cells. This pattern suggests that IL-6 produced
and secreted by the aMFH acted as a growth factor for
plasma cells as well as tumour cells. Documenting a high
density of polyclonal plasma cells in close proximity to
tumour cells supports this hypothesis, suggesting an ex-
planation for the formation of one tumour by two cell
populations of different origin.

Collectively, the patient’s history and described findings
show that the signs and symptoms of our case reflect the
effects of chronic IL-6 exposure. It identifies IL-6 as the
pathogenic factor for paraneoplastic signs and symptoms
in aMFH. Finally, it illustrates that complete response to

Fig. 1 MRI and histology of Baker’s cyst

![MRI and histology of Baker’s cyst](image-url)
IL-6 blockade in a case resistant to TNF neutralization should prompt a second diagnostic workup.

**Rheumatology key message**

- Neutralization of IL-6 by tocilizumab induces complete clinical remission and controls the growth of popliteal angiomatoid malignant fibrous histiocytoma.

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