patients, 81 infliximab naive RA patients and 47 healthy subjects as controls. At the same time and apart from the purposes of that study, we also had done a pathergy test in those subjects who agreed to participate, with the aim of determining the effect of the pathergy phenomenon on the response of BS patients to the tuberculin test. Informed consent was obtained from all subjects. The study was approved by the ethical committee of Istanbul University, Cerrahpasa Medical School.

Eighty BS and 61 RA patients and 38 healthy controls participated. The tuberculin test was administered with the Mantoux technique, using 5 IU of purified protein derivative (PPD) solution, which was injected intradermally into the forearm by a nurse. The pathergy test was done at three sites on each forearm by inserting six sterile 20-gauge needles intradermally, on the same day as the tuberculin test. Both the tuberculin test and the pathergy reaction were evaluated 48h later, by two independent observers in a blinded manner. Subjects put their arms through a curtain and their hands were covered to prevent the observers from recognizing the subjects, or any deformities revealing the diagnosis. PPD reaction was evaluated by measuring the transverse diameter of the induration. A positive pathergy test was defined as a papule or a pustule at the insertion site of the needle. The number of subjects with a positive PPD test (≥10 mm) in each group was compared and the relationship between PPD positivity and the pathergy phenomenon was sought.

The number of patients with a positive pathergy reaction, a positive PPD test and the mean PPD induration of each group are provided in Table 1. The mean diameter of the PPD induration was lower among RA patients (H$_{diff}$ = 20.1, $P < 0.001$, Kruskal–Wallis) when compared with BS patients and healthy controls. The mean indurations in BS patients and healthy controls were similar (H$_{diff}$ = 2.0, $P = 0.163$, Kruskal–Wallis). Inter-group comparisons revealed that mean PPD induration was similar among BS patients and healthy controls (Mann–Whitney $U = 1207$, $P = 0.163$). PPD indurations in both BS patients and healthy controls were higher than in RA patients (Mann–Whitney $U = 1595$, $P < 0.001$ and Mann–Whitney $U = 568.5$, $P = 0.001$, respectively).

The number of patients with a positive PPD test was also lower among RA patients than the other two groups ($\chi^2 = 19.246$, $P < 0.001$). Inter-group comparisons showed that the frequency of PPD positivity was similar among BS patients and healthy controls ($P = 0.2$), and higher in both BS patients and healthy controls when compared with RA patients ($P = 0.002$ and $P < 0.001$, respectively).

Then, we looked at the association between having a positive pathergy test and the size of the PPD reaction. The mean PPD induration was similar among BD patients with a positive pathergy test and among those with a negative test ($9.8 \pm 7.1$ vs $11.9 \pm 7.7$ mm; $P = 0.316$). The number of patients with a positive PPD test was also similar among BS patients with and without a positive pathergy reaction (12/18, 67% vs 38/62, 63%; $P = 0.79$). Forty-seven of the BS patients were using immunosuppressive drugs such as AZA and CsA. The frequency of a positive PPD test was not different between the patients who were receiving immunosuppressives and those who were not (30/47 vs 21/33, $P = 0.6$). Similarly, the mean PPD induration was not different between those who were receiving immunosuppressives and those who were not (11.3 ± 7.5 vs 11.5 ± 7.5; $P = 0.947$).

The frequency of a positive pathergy test among BD patients was somewhat lower than previously reported [6]. The patients we included were patients who were being followed in our clinic for some time. This might have resulted in a lower frequency of pathergy positivity when compared with a newly diagnosed group of patients.

Our findings showed that the PPD reaction was not augmented among BS patients and its induration size was not affected by having a positive pathergy test.

### Table 1. Number of patients with a positive pathergy reaction, a positive PPD test and the mean PPD induration of each group

<table>
<thead>
<tr>
<th>Group</th>
<th>BS (n = 80)</th>
<th>RA (n = 61)</th>
<th>Healthy controls (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A positive pathergy test (%)</td>
<td>18/80 (23)</td>
<td>4/61 (7)</td>
<td>1/38 (3)</td>
</tr>
<tr>
<td>A positive PPD test (%)</td>
<td>50/80 (63)</td>
<td>21/61 (34)</td>
<td>29/38 (76)</td>
</tr>
<tr>
<td>Mean PPD induration (mm) (±S.D.)</td>
<td>11.4 ± 7.6</td>
<td>6.8 ± 7.1</td>
<td>13.6 ± 7.3</td>
</tr>
</tbody>
</table>

Rheumatology key message

- The PPD reaction is not augmented in BS patients and it is not affected by the pathergy phenomenon.

Disclosure statement: The authors have declared no conflicts of interest.

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Occurrence of cold agglutinin disease in RA patient during etanercept therapy successfully treated with rituximab

Sir, Cold agglutinin disease (CAD) is characterized by the presence of cold agglutinins (CAs), directed against the I/i carbohydrate antigens on the surface of red blood cells (RBCs), causing haemagglutination and haemolysis [1]. Pathogenic CAs are generally of the IgM isotype and derive from monoclonal B-cell expansions [2], exclusively encoded by the VH4-34 segment causing haemagglutination and haemolysis [1]. Pathogenic CAs are generally of the IgM isotype and derive from monoclonal B-cell expansions [2], exclusively encoded by the VH4-34 segment causing haemagglutination and haemolysis [1]. Pathogenic CAs are generally of the IgM isotype and derive from monoclonal B-cell expansions [2], exclusively encoded by the VH4-34 segment causing haemagglutination and haemolysis [1].

Chronic CAD is usually idiopathic, but it has been occasionally described in patients with autoimmune diseases such as SLE, RA, adult onset Still’s disease, SS, SSc or lymphoproliferative disorders [4, 5]. It has been shown that the primary form frequently represents a lymphoproliferative bone marrow disorder characterized by clonal expansion of B cells [4, 5]. Conventional treatment with corticosteroids, alkylating agents, immunosuppressive drugs, IFN-α or cladribine are usually ineffective in CAD [6]. Conversely, the chimeric monoclonal anti-CD20 antibody rituximab, that is currently used for the treatment of non-Hodgkin
lymphoma and refractory RA, has been shown to induce remission in >50% of CAD patients [7].

Here, we report a case of RA developing CAD during a course with an anti-TNF-\(\alpha\) agent successfully treated with rituximab.

The patient, a 52-yr-old woman, affected by RA (ACR 1987 criteria) since 1988, had been treated with both prednisolone 5–7.5 mg/day and low dose of MTX (7.5–15 mg/week) until 1996, and successively with both prednisolone 5–7.5 mg/day and LEF 20 mg/day until 1997, because of lack of efficacy. For the occurrence of gastrointestinal adverse events and inefficacy, the patient started etanercept 25 mg/once a week, achieving a marked improvement of the arthritis with remission [28-joint disease activity score (DAS28) <2.6] at month 6. Nevertheless, during this course the patient showed laboratory abnormalities including mild leucopenia with neutropenia and anaemia, that worsened progressively causing the withdrawal of treatment at week 40 [white blood counts (WBCs) 4.0 \(\times 10^3/\mu\)l, neutrophils 1.7 \(\times 10^3/\mu\)l, RBCs 3.3 \(\times 10^6/\mu\)l, Hb 11.0 g/dl]. At this time, laboratory data showed clumps of agglutinated red cells on blood smear taken at room temperature, positive direct Coombs test (DAT) using polyspecific anti-serum, high CA titre of 1:512 with no evidence of clonal lymphoproliferation as assessed by bone marrow histology. Finally, flow-cytometric analysis revealed IgM-class antibodies against antigen I on RBCs. The patient was treated with prednisolone (1 mg/kg/day then tapered to 0.25 mg/kg/day) and CSA (3 mg/kg/day). Both a worsening of anaemia and a relapse of polyarthritis were detected after 2 months of partial response defined according to Zaja et al. [8]. Rituximab was given at 1000 mg intravenously for two courses on days 1 and 14 according to the Reflex study protocol. The patient showed rapid improvement in arthritis achieving a good response according to EULAR criteria at day 14, and persistent remission between months 2 and 6. No infusion-related adverse events were pointed out. Complete recovery of haemoglobin level, reticulocyte count, leucocyte count, BUN, lactate dehydrogenase, bilirubin and haptoglobin level and reduction of CA titre at month 3 were recorded, without any new change 6 month after rituximab therapy (Table 1).

The efficacy of rituximab in patients with CAD has also been recently reported by other groups [8], with response rates and response duration very similar to those reported in follicular lymphoma and other indolent CD20+ B-cell lymphomas [9, 10]. To our knowledge, our report documented for the first time the occurrence of CAD in a RA patient during treatment with etanercept, confirming the efficacy of rituximab when CAD is refractory to conventional treatment. Moreover, the occurrence of leucopenia and neutropenia, that have not been described in primary CAD [5, 6] may be considered independent adverse events during etanercept course successfully treated with rituximab as well.

### Table 1. Laboratory and clinical changes in RA patient with CAD treated with rituximab infusions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>14th day</th>
<th>3rd month</th>
<th>6th month</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC ((\times 10^9/\mu)l)</td>
<td>4.4</td>
<td>5.1</td>
<td>5.7</td>
<td>6.8</td>
</tr>
<tr>
<td>RBC ((\times 10^12/\mu)l)</td>
<td>2.8</td>
<td>2.8</td>
<td>4.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Haemoglobin (g/dl; 12–16)</td>
<td>9.1</td>
<td>9.7</td>
<td>13.1</td>
<td>14.0</td>
</tr>
<tr>
<td>MCV (fl; 80–99)</td>
<td>100.5</td>
<td>98.9</td>
<td>92.2</td>
<td>90.0</td>
</tr>
<tr>
<td>Reticulocyte count (%; 0.5–2.5)</td>
<td>9.0</td>
<td>6.2</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Neutrophils ((\times 10^9/\mu)l)</td>
<td>2.2</td>
<td>2.8</td>
<td>2.7</td>
<td>4.4</td>
</tr>
<tr>
<td>γGT (UI/l; 5–36)</td>
<td>56</td>
<td>34</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>ALP (UI/l; 35–104)</td>
<td>115</td>
<td>81</td>
<td>73</td>
<td>79</td>
</tr>
<tr>
<td>LDH (UI/l; 240–480)</td>
<td>1008</td>
<td>902</td>
<td>300</td>
<td>269</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl; 0–1)</td>
<td>1.54</td>
<td>1.24</td>
<td>0.42</td>
<td>0.60</td>
</tr>
<tr>
<td>Haptoglobin (mg/dl; 30–200)</td>
<td>0</td>
<td>10</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>Cold agglutinin titre ((\leq 1:32))</td>
<td>1.512</td>
<td>1.512</td>
<td>1.128</td>
<td>1.128</td>
</tr>
<tr>
<td>CRP (mg/l; &lt;5)</td>
<td>1.8</td>
<td>1.7</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>DAS28</td>
<td>5.7</td>
<td>3.1</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

MCV: mean corpuscular volume; γGT: gamma glutamyl transferase; LDH: lactate dehydrogenase.

The relation between CAs and lymphoproliferative disorders [4, 5], and the lack of consensus on the risk of lymphoma with anti-TNF-\(\alpha\) agents, may suggest CAs evaluation as an additional safety parameter in RA patients taking TNF-\(\alpha\) inhibitors.

### Rheumatology key message
- Rituximab can cure cold agglutinin disease in RA patients refractory to conventional treatment.

### Disclosure statement
The authors have declared no conflicts of interest.

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Imatinib for the treatment of refractory, diffuse systemic sclerosis

Sir, We report on the beneficial, 6-month compassionate use of the tyrosine kinase inhibitor imatinib mesylate (Gleevec) in a 24-yr-old woman with severe diffuse systemic sclerosis of 7 yrs duration. The patient presented in 1999 with Raynaud’s phenomenon, followed shortly after by widespread diffuse scleroderma. A year later she was seen at the Royal Free Hospital, having a modified Rodnan skin score of 39 (maximum 51), muscle weakness, flexed hands and evidence of early interstitial lung fibrosis. She received 6-monthly intravenous (IV) pulses of cyclophosphamide, resulting in a decrease of skin score to 30. Subsequently, she received imatinib therapy with azathioprine (2 mg/kg daily) for 16 months. Despite a further 16 months of treatment with mycophenolate mofetil and bimonthly 5-day...