No primary association of MICA polymorphism with systemic lupus erythematosus

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Objective. To replicate the described association between MHC class I chain-related A (MICA) gene polymorphism and susceptibility to systemic lupus erythematosus (SLE).

Methods. MICA transmembrane microsatellite polymorphism was genotyped using a polymerase chain reaction (PCR)-based method. Genotyping of HLA-B* and DRB1* was performed using PCR and detection with a reverse sequence-specific oligonucleotide (SSO) probe system. Combined data for these three loci (HLA-B*, DRB1* and MICA) were obtained from a total of 333 patients and 361 healthy controls.

Results. Significant association with B*08 \( [P<10^{-7}, \text{odds ratio (OR)} 3.17, 95\% \text{ confidence interval (CI)} 2.02–5.00] \), DRB1*0301 \( (P<10^{-7}, \text{OR} 2.07, 95\% \text{ CI} 1.59–2.68) \) and MICA5.1 \( (P=0.01, \text{OR} 1.23, 95\% \text{ CI} 1.04–1.46) \) was observed. The combinations DRB1*0301-MICA5.1-B8 and HLA-DRB1*0301-B*08-positive and MICA5.1-negative were more frequent among SLE patients \((11.4 \% \text{ vs} 3.3\% \text{ in healthy controls, } P=3.9\times10^{-5}, \text{OR} 3.76, 95\% \text{ CI} 1.85–7.73, \text{and} 6.9 \% \text{ vs} 1.7\%, P=0.0007, \text{OR} 4.32, 95\% \text{ CI} 1.68–13.10, \text{respectively})\). Additionally, individuals who were HLA-DRB1*0301-B*08-negative and MICA5.1-positive were less frequent among patients \((22.2 \% \text{ vs} 31.3\% \text{ in healthy controls, } P=0.007, \text{OR} 0.63, 95\% \text{ CI} 0.44–0.89) \) and the magnitude of the OR was similar to that obtained in individuals negative for all the three factors \((\text{OR} 0.69, 95\% \text{ CI} 0.50–0.94) \). Further analysis performed to detect independent association strongly suggested that the association between MICA5.1 and SLE is secondary to the linkage disequilibrium of this allele with B*08.

Conclusions. Our results do not support an independent association of MICA gene polymorphism with susceptibility to SLE.

Key words: MICA, HLA-DRB1, HLA-B, SLE, Susceptibility.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a complex pathogenesis involving multiple genetic and environmental factors. Production of multiple autoantibodies and immune complex deposits causing tissue damage is a characteristic of this disease. Human major histocompatibility (HLA) class I and class II molecules have been described as genetic risk factors for many autoimmune diseases [reviewed in 1–3]. Two HLA class II haplotypes, DRB1*0301-DQA1*0501-DQB1*0201 and DRB1*1501-DQA1*0102-DQB1*0602, have been consistently associated with susceptibility to SLE in different Caucasian populations [4–6]. Additionally, several studies have described an association of HLA-B8 with susceptibility to SLE [7], and other genes located in the HLA region, such as TNFα, C2 and C4 have also been associated with susceptibility to the disease [reviewed in 8,9].

A family of non-classical HLA genes known as major histocompatibility complex class I chain-related gene A (MICA) has been located 46 kb centromeric to the HLA-B gene. The MICA gene has a full length of 11.7 kb and encodes a stress-inducible molecule with three extracellular domains (α1, α2 and α3), a transmembrane (TM) region and a cytoplasmic tail (CY) [10,11], and it shows preferential expression in fibroblasts and epithelial cells. The MICA chain folds similarly to typical class I chains and may have the capacity to bind peptides or other short ligands. A microsatellite polymorphism consisting of a variable number of GCT repeats encoding 4, 5, 6, 7, 9 or 10 alanine residues and located on the MICA exon 5 (TM segment) has been identified. Additionally, the MICA A5.1 allele presents a nucleotide insertion (G) between the second and third triplet repeats, resulting in a premature stop codon [12–14].

The location of the MICA gene in the HLA region and its association with other autoimmune diseases suggests the MICA gene as a possible candidate gene for the development of SLE. A recent study reported an independent contribution of the MICA TM polymorphism to susceptibility to SLE in an Italian population [15]. The aim of the present study was to investigate whether the MICA TM polymorphism, as well as HLA class I (locus B) and class II (locus DRB1*), influences genetic predisposition to SLE in a large Spanish cohort of patients.

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Materials and methods

Subjects

A total of 574 SLE patients (13% men and 87% women), meeting the American College of Rheumatology (ACR) criteria for SLE [16, 17], were recruited from five Spanish hospitals: Hospital Virgen de las Nieves and Hospital Clinico San Cecilio (Granada), Hospital Virgen del Rocío (Seville), Hospital Xeral-Calde (Lugo) and Hospital Carlos-Haya (Malaga). The mean (s.d.) age of the SLE patients at diagnosis was 43 ± 13.9 yr and the mean age at onset was 32 ± 15 yr. A total of 934 blood bank and bone marrow donors from the corresponding cities were included as healthy controls. The patient and control groups were both of Spanish Caucasian origin and were matched for age and sex. Samples were obtained from subjects after they had given written informed consent. The study was approved by all local ethical committees of the corresponding hospitals.

MICA genotyping

Genomic DNA was isolated from anticoagulant-treated peripheral blood mononuclear cells using standard methods. Genotyping of the MICA TM microsatellite polymorphism was performed using a polymerase chain reaction (PCR)-based method as previously described [18]. Briefly, primer sequences were MICA 5F 5'-CCT TTT TTT CAG GGA AAG TGC-3' and MICA 5R 5'-CCT TAC CAT CTC CAG AAA CTG C-3'. The reverse primer was labelled at the 5' end with 6-FAM dye. PCR products were electrophoresed in an ABI Prism 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and their sizes were determined using the Genescan 672 software (Applied Biosystems).

HLA genotyping

Genotyping for HLA-B*, MICA and DRB1* was carried out using a reverse dot-blot kit with sequence-specific oligonucleotide (SSO) probes (Dynal RELITM SSO HLA-B and DRB1* typing kits; Dynal Biotech, Bromborough, UK). When necessary, high resolution typing of HLA-DRB1*03 samples was performed using Dynal AllSetTM SSP DRB1*03.

Genotyping of the three loci HLA-B*, MICA and DRB1* was performed in 333 SLE patients and 361 healthy controls.

Statistical analyses

Allelic and phenotypic frequencies of the HLA markers studied were obtained by direct counting. Statistical analysis to compare distributions was performed with the χ² test. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated according to Wolf’s method. The software used was Statcalc program (Epi Info 2002; Centers for Disease Control and Prevention, Atlanta, GA, USA). P-values below 0.05 were considered statistically significant. The P-values were corrected (Pc) according to the Bonferroni method for the MICA TM alleles (n = 5). To detect the strongest association for data in Table 2, the test described by Svegaard and Ryder was used and the P-values were corrected as recommended by these authors [19]. The correction factor used in each case is shown in parentheses.

Results

No significant differences in the frequency of the different alleles of the three genes studied were observed among patient groups or among control groups from the five cohorts. Hence we combined the five cohorts to form a SLE case–control group, which was used in further analyses. The control study population was found to be in Hardy–Weinberg equilibrium for all the loci studied.

Table 1 shows the distribution of the MICA alleles in Spanish SLE patients and controls. As has been found in other Caucasian populations [15, 18], in our population we found five alleles: A4, A5, A5-1, A6 and A9; the MICA allele displaying the highest frequency in both patient and control groups was A6 (35.8 and 38.9% respectively). There was a significant deviation in the distribution of the alleles of MICA that distinguished patient and control groups (P = 0.007, χ² test with a 5 × 2 contingency table). This significant deviation corresponded to a higher frequency of MICA5.1 [28.1% vs 24.0% in the control group; P = 0.01, (5)P = 0.05, OR 1.23, 95% CI 1.04–1.46] and a lower frequency of MICA5 among SLE patients [10.9% vs 14.1% in the control group; P = 0.009, (5)P = 0.045, OR 0.74, 95% CI 0.59–0.94]. No significant differences in the distribution of individuals homozygous for MICA5.1 were observed when patient and control groups were compared (12.0 vs 12.3%, P > 0.05).

Regarding HLA typing, the HLA-B* gene was genotyped in 399 SLE patients and 385 control subjects. The allelic frequency of HLA-B*08 was significantly higher in patients (11.0% vs 3.8% in the control group, P < 10⁻⁴, OR 3.17, 95% CI 2.02–5.00). Additionally, the HLA-DRB1* was genotyped in 459 SLE patients and 522 healthy controls and, as in other studies, the allelic frequency of HLA-DRB1*0301 was higher in patients (20.4% vs 11.0% in controls, P < 10⁻⁴, OR 2.07, 95% CI 1.59–2.68). The allelic frequency of HLA-DRB1*15 was higher in SLE patients (12.0 vs 9.4% in the control group) but the difference did not reach statistical significance (P = 0.06). The distribution of HLA-DRB1*08 was similar in patients and controls (3.4% vs 3.1%, P = 0.7).

Strong linkage disequilibrium between B*08 and both MICA5.1 and DRB1*0301 was observed in our control population [P(9) = 0.00018 and P(9) < 10⁻⁶, respectively]. Nevertheless, no significant linkage disequilibrium between MICA5.1 and DRB1*0301 was observed in our control group (P = 0.4). No significant linkage disequilibrium between MICA5.1 and DRB1*15 was observed among B*08- or DRB1*0301-negative controls [P(9) > 0.05 in all cases].

We performed further analysis to better define the contribution of each marker to susceptibility to SLE. Table 2 shows data for the four phenotypic combinations of the three factors studied two by two. The highest OR, taking into account two positive risk factors, was for the combination B*08-positive–DRB1*0301-positive (P < 10⁻⁷, OR 4.18, 95% CI 2.40–7.36) and the lowest OR was for the combination B*08-negative–DRB1*0301-negative (P < 10⁻⁷, OR 0.43, 95% CI 0.31–0.59). Additionally, frequencies of individuals who were B*08-positive–MICA5.1-negative and individuals who were DRB1*0301-positive–MICA5.1-negative were higher in patients (7.8% vs 1.7% in controls, P = 7.7 × 10⁻⁵, OR 5.07 95% CI 2.05–15.01, and 19.5% vs 13.0% in controls, P = 0.06).
Table 2. Contribution of B*08/MICA5.1, DRB1*0301/MICA5.1 and B*08/DRB1*0301 to the risk of SLE, comparing patients and controls in a 2 × 2 analysis

<table>
<thead>
<tr>
<th>B*08</th>
<th>MICA5.1</th>
<th>SLE patients n = 396 (%)</th>
<th>Healthy controls n = 364 (%)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>56 (14.1)</td>
<td>21 (5.8)</td>
<td>0.0001</td>
<td>2.69 (1.55–4.70)</td>
</tr>
<tr>
<td></td>
<td>−</td>
<td>31 (7.8)</td>
<td>6 (1.7)</td>
<td>7.7 × 10⁻⁵</td>
<td>5.07 (2.05–15.01)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>116 (29.3)</td>
<td>124 (34.1)</td>
<td>NS</td>
<td>0.68 (0.48–0.95)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>193 (48.7)</td>
<td>213 (58.5)</td>
<td>0.007</td>
<td>0.67 (0.50–0.91)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MICA5.1</th>
<th>DRB1*03</th>
<th>SLE patients n = 333 (%)</th>
<th>Healthy controls n = 361 (%)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>55 (16.5)</td>
<td>27 (7.5)</td>
<td>0.0002</td>
<td>2.45 (1.47–4.10)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>83 (24.9)</td>
<td>119 (33.0)</td>
<td>0.02</td>
<td>0.68 (0.48–0.95)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>65 (19.5)</td>
<td>47 (13.0)</td>
<td>0.02</td>
<td>1.62 (1.06–2.49)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>130 (39.0)</td>
<td>168 (46.5)</td>
<td>0.05</td>
<td>0.74 (0.54–1.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B*08</th>
<th>DRB1*0301</th>
<th>SLE patients n = 388 (%)</th>
<th>Healthy controls n = 386 (%)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>69 (17.8)</td>
<td>19 (4.9)</td>
<td>&lt;10⁻⁷</td>
<td>4.18 (2.40–7.36)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>71 (18.3)</td>
<td>59 (15.3)</td>
<td>NS</td>
<td>0.68 (0.48–0.95)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>18 (4.6)</td>
<td>10 (2.6)</td>
<td>NS</td>
<td>0.74 (0.54–1.01)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>230 (59.3)</td>
<td>298 (77.2)</td>
<td>10⁻⁷</td>
<td>0.43 (0.31–0.59)</td>
</tr>
</tbody>
</table>

NS, not significant.

Table 3. Contribution of B*08/MICA5.1/DRB1*0301 to susceptibility to SLE

<table>
<thead>
<tr>
<th>DRB1*0301</th>
<th>MICA5.1</th>
<th>B*08</th>
<th>SLE patients n = 333 (%)</th>
<th>Healthy controls n = 361 (%)</th>
<th>P</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>38 (11.4)</td>
<td>12 (3.3)</td>
<td>3.9 × 10⁻⁵</td>
<td>3.76 (1.85–7.73)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>−</td>
<td>17 (5.1)</td>
<td>15 (4.2)</td>
<td>NS</td>
<td>0.74 (0.54–1.01)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>+</td>
<td>23 (6.9)</td>
<td>6 (1.7)</td>
<td>0.0007</td>
<td>4.32 (1.68–13.10)</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>−</td>
<td>41 (12.3)</td>
<td>41 (11.4)</td>
<td>NS</td>
<td>0.74 (0.54–1.01)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>+</td>
<td>9 (2.7)</td>
<td>6 (1.7)</td>
<td>NS</td>
<td>0.74 (0.54–1.01)</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>−</td>
<td>74 (22.2)</td>
<td>113 (31.3)</td>
<td>0.007</td>
<td>0.63 (0.44–0.89)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>+</td>
<td>7 (2.1)</td>
<td>2 (0.6)</td>
<td>NS</td>
<td>0.74 (0.54–1.01)</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>−</td>
<td>123 (36.9)</td>
<td>166 (46.0)</td>
<td>0.01</td>
<td>0.69 (0.50–0.94)</td>
</tr>
</tbody>
</table>

NS, not significant.

P = 0.02, OR 1.62, 95% CI 1.06–2.49). Nevertheless, frequencies of individuals who were B*08-negative–MICA5.1-positive and individuals who were DRB1*0301-negative–MICA5.1-positive were lower among patients (29.3 vs 34.1% in the control group, P > 0.05, and 24.9 vs 33.0 in the control group, respectively, P = 0.02, OR 0.68 95% CI 0.48–0.95).

Table 3 shows data for the eight possible phenotypic combinations of the three risk factors studied. The highest OR (4.32, 95% CI 1.68–13.10) found was for the combination B*08 positive–MICA5.1-negative–DRB1*0301-positive, whereas the lowest OR found was for the combination B*08-negative–MICA5.1-positive–DRB1*0301-negative (0.63, 0.44–0.89). Next, we investigated the association of DRB1*0301-MICA5.1-B*08 to evaluate which of these factors are likely to be the responsible of the association, using the test recommended by Sverjgaard and Ryde [19]. In this analysis, MICA5.1 did not show any association with SLE in B*08-positive (P = 0.2) or in B*08-negative (P = 0.8) individuals or in DR*0301-positive (P = 0.2) or DR*0301-negative (P = 0.6) individuals, suggesting that MICA5.1 is not an independent risk factor for SLE. On the contrary, B*08 was associated with SLE in MICA5.1-positive [P(6) = 0.0012, OR 5.70, 95% CI 2.07–17.03] and negative [P(6) = 0.00042, OR 2.92, 95% CI 1.65–5.20] and MICA5.1-negative [P(6) = 0.02, OR 1.79, 1.13–2.84] individuals. Regarding the independent contribution of B*08 and DRB1*0301, the frequency of B*08 was not increased in DRB1*0301-positive individuals (P = 0.1) and was probably only increased in DRB1*0301-negative [P = 0.02, OR (6) = 0.12, OR 1.56 95% CI 1.04–2.34] individuals. Conversely, the frequency of DRB1*0301 was increased in B*08-positive individuals [P(6) = 0.0018, OR 2.98, 95% CI 1.55–5.77] and probably only increased in B*08-negative individuals [P = 0.03, OR (6) = 0.18, OR 2.33, 95% CI 1.00–5.54]. Using the test recommended by Sverjgaard and Ryde [19], associations with SLE of B*08 and DRB1*0301 were stronger than the association of MICA5.1 [P(6) = 0.00036 and P(6) = 0.024 respectively]. Nevertheless, no significant differences in the strength of the association of B*08 and DRB1*0301 was observed (P = 0.4). Finally, strong linkage disequilibrium between B*08 and both MICA5.1 and DRB1*0301 was observed also in the patient group [P(9) = 0.00072 and P(9) < 10⁻⁶, respectively]. Nevertheless, no significant linkage disequilibrium between MICA5.1 and DRB1*0301 was observed among patients (P = 0.2) or among controls (P = 0.4), even after stratification for B*08 [P(9) > 0.05 in all cases]. Additionally, there was no evidence for an association of MICA5.1 with SLE among B*08 positive–DRB1*0301-positive
individuals ORs were very similar for MICA5.1-negative and MICA5.1-positive individuals (4.32 vs 3.76).

Discussion

The MHC region has been associated with susceptibility to SLE in many studies. However, the literature concerning association with HLA-SLE is often in disagreement regarding the genes involved in the susceptibility [20, 21]. This could be due to confounding factors caused by strong linkage disequilibrium in the region.

Recently, a study suggesting an independent contribution of the MICA TM polymorphism to susceptibility to SLE in an Italian population was reported [15]. This case–control study was performed in a relatively small group of individuals (48 patients and 158 controls) and the authors reported a positive association of susceptibility to SLE with both MICA5.1 and MICA5 alleles and a negative association with MICA9. Gambelunghe et al. [15] reported an association between HLA-B8 and SLE in the Italian population. They also found strong linkage disequilibrium between HLA-B8 and MICA5.1, indicating that HLA-B8 was not significantly and independently associated with SLE. However, they did not perform any analysis to detect which of these genes showed the strongest association. We think this may explain the discrepant results obtained in the present work. Our study failed to confirm an independent association between MICA and SLE.

The MICA5.1 allele showed an association with SLE susceptibility in the one-marker analysis, although the OR (1.23) found was lower than those obtained for B*08 (3.17) and DRB1*0301 (2.07). Tables 2 and 3 show that the presence of MICA5.1 is neutral if B*08 is absent, or even protective if DRB1*0301 or both B*08 and DRB1*0301 are absent. The magnitude of the OR (0.63), as given by the simultaneous presence of MICA5.1 and absence of both B*08 and DRB1*0301, was similar to that given by the absence of these three factors (0.69). Additionally, analysis performed to detect independent association strongly suggests that the association described between MICA5.1 and SLE is secondary to the linkage disequilibrium of this allele with B*08. Regarding MICA5, we observed a lower the frequency of this allele among patients. This contradiction with the previous study could be due to a difference in linkage disequilibrium between HLA-B* and MICA in Italian and Spanish populations and, in any case, the contrary effect found for MICA5 in both populations does not support any association of this allele. No differences in the distribution of the allele MICA9 were observed to allow comparison between patient and control groups.

Our results confirm previous findings regarding the association of HLA-B*08 and DRB1*0301 with susceptibility to SLE [reviewed in 1–5]. Data obtained in the present study are not conclusive enough to clarify which of these two markers is more strongly associated with the disease. Tables 2 and 3 show a strong positive association of susceptibility to the disease with the presence of both factors and a strong negative association with their absence. Nevertheless, individuals positive only for one of these factors are in the minority, although they are not significantly increased among patients. Additional analysis performed to detect independent association did not provide strong evidence supporting any hypothesis because several critical P-values are not significant after correction, both markers show a similar strength of association and they are in strong linkage disequilibrium. Regarding other class II specificities associated with SLE in different populations, as already described in other Caucasian populations, only a weak increase in the frequency of HLA-DRB1*1501 was observed in our series of patients and the distribution of DRB1*08 was very similar in both patients and controls.

In conclusion, our results do not support an independent association between MICA and SLE and are in agreement with the previous finding reporting an association with B*08 and DRB1*0301.

Acknowledgements

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References

Clinical Vignette

The patient, a 69-yr-old man, had seropositive erosive rheumatoid arthritis (RA) diagnosed in 1977. He failed on the conventional disease-modifying agents of salazopyrin and methotrexate. Complications of Felty’s syndrome (splenomegaly, neutropenia) and osteoporosis developed during his disease course. In 1997 he developed skin ulceration on the right first web space, left medial malleolus and right medial malleolus.

Clinically, his lower limb pulses were palpable with no venous insufficiency. Peripheral nerves were intact. Arterial pulse pressures were normal. Blood glucose and cholesterol were within normal limits. Anti-neutrophil cytoplasmic antigens were negative. Serum inflammatory markers were elevated, with erythrocyte sedimentation rate (ESR) at 90 mm/h and C-reactive protein (CRP) at 67 mg/dl. While pyoderma granulomatus was considered, following a dermatological review a clinical diagnosis of vasculitic ulceration of the skin associated with Felty’s syndrome was made in the light of his previous features. Treatment was high-dose corticosteroids and oral cyclophosphamide. There was an initial improvement in the size of the ulcers. After 6 months of therapy, cyclophosphamide was switched to azathioprine. With reduction in corticosteroid, the ulcers again deteriorated. Treatment was adjusted with the administration of intravenous prostaglandins and pulse cyclophosphamide. Subsequent maintenance therapy was oral cyclophosphamide.

In 2001, due to inefficacy, treatment was changed to infliximab (dose 3 mg/kg every 8 weeks). Over the subsequent months, there was a dramatic improvement at the right medial malleolus and complete healing at the other two sites. The patient’s joint symptoms also diminished, although ESR remained elevated at 30 mm/h and neutropenia persisted. Due to the development of a septic prosthetic joint, infliximab therapy was discontinued. During this time there was a significant deterioration in the areas of ulceration. Improvement was noted again when anti-TNF therapy, this time adalimumab, was reintroduced with prophylactic antibiotic cover.

Anti-TNF therapy can be an effective treatment for systemic large- and medium-vessel vasculidites. Cutaneous manifestations also respond with pyoderma gangrenosum healing in patients with inflammatory bowel disease. There appears to be increased blood flow due to improved endothelial vasomotor responses following anti-TNF therapy [1]. Adverse event reporting has shown paradoxically that these agents can be associated with the development of new-onset vasculitides [2]. The mechanism of this is unclear. Our case highlights a role for anti-TNF therapy in the treatment of cutaneous ulceration secondary to RA/Felty’s syndrome.

The authors have declared no conflicts of interest.

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FIG. 1. Serial photographs of the ulcer at the right medial malleolus in a patient with rheumatoid arthritis following commencement on infliximab therapy.