ation, since the corrected P value was not significant. In contrast to the decreased frequency of DR52 found in English patients with primary antiphospholipid syndrome (6), we found a higher frequency of this antigen in our patients. Another difference between English and Mexican patients is that 92% of the English patients were positive for the supertypic antigen HLA–DR53, whereas in Mexicans the frequency of this antigen was similar in patients and controls. Comparable findings were noted with the HLA–DR4 antigen, which had a frequency of 76.9% in English patients whereas it was found in only 35% of our Mexican patients and 42% of Mexican controls (results not shown). Regarding the HLA–DQ region, Arnett et al (4) reported that HLA–DQ7 is associated with the presence of lupus anticoagulant, a related aPL, in black and white SLE patients in the US. We found no association with HLA–DQ7 in our primary antiphospholipid syndrome patients, all of whom had aPL, but found that all DRB1*1101 or DRB1*1201 positive patients in whom DQ variants were detected were also DQB1*0301 positive. In Italian SLE patients, an association between anticardiolipin antibodies and HLA–DR7 was found (5). We did not identify such an association in our primary antiphospholipid syndrome patients, although we did find it in our Mexican SLE patients with secondary antiphospholipid syndrome (Vargas-Alarcon G et al: unpublished results). This difference between patients with the primary and those with the secondary antiphospholipid syndrome supports the notion that the primary antiphospholipid syndrome is a distinct entity and not merely a phase in the course of SLE.

Two of our 6 DR5 negative primary antiphospholipid syndrome patients had DR8 and 2 had DR3. The DR5 allele has the coded sequence of the DRB1 region with marked homology with DR8 and DR3 alleles, which is in accord with the notion that all 3 alleles belong to the DR52 family. The DR3 and DR5 alleles share amino acids 9–13 of the first hypervariable region from the DRB1 gene (Glu, Tyr, Ser, Thr, Ser), whereas the DR8 allele differs only at position number 13 (10,11). This sequence could be crucial in the antigen recognition that leads to the production of aPL, since it is located on the floor of the antigen-recognition site of the MHC molecule (12). The finding that 19 of 21 Mexican patients with primary antiphospholipid syndrome had alleles belonging to the DR52 family, while a similar proportion of English patients had alleles belonging to the DR53 family, suggests that they result from different point mutations. It also suggests that the development of aPL in primary antiphospholipid syndrome may be antigen driven, whereas in SLE these autoantibodies may be genetically determined, since, in at least 2 different ethnic groups, they were associated with HLA–DR7.

Our findings indicate an association of DR5 (DRB1*1201) with susceptibility to primary antiphospholipid syndrome in Mexicans. The relevant gene appears to be located near the DRB1 gene and to belong to the DR52 family, whose related alleles share a sequence that could be relevant to the antigen recognition site. Additional sequence analysis of the HLA–DQ alleles could help define their role in the primary antiphospholipid syndrome in Mexican patients.

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Cytarabine therapy for refractory cutaneous lupus

Treatments for cutaneous lupus include antimalarials, topical and systemic corticosteroids, azathioprine, methotrexate and cyclophosphamide, and occasionally, dap-

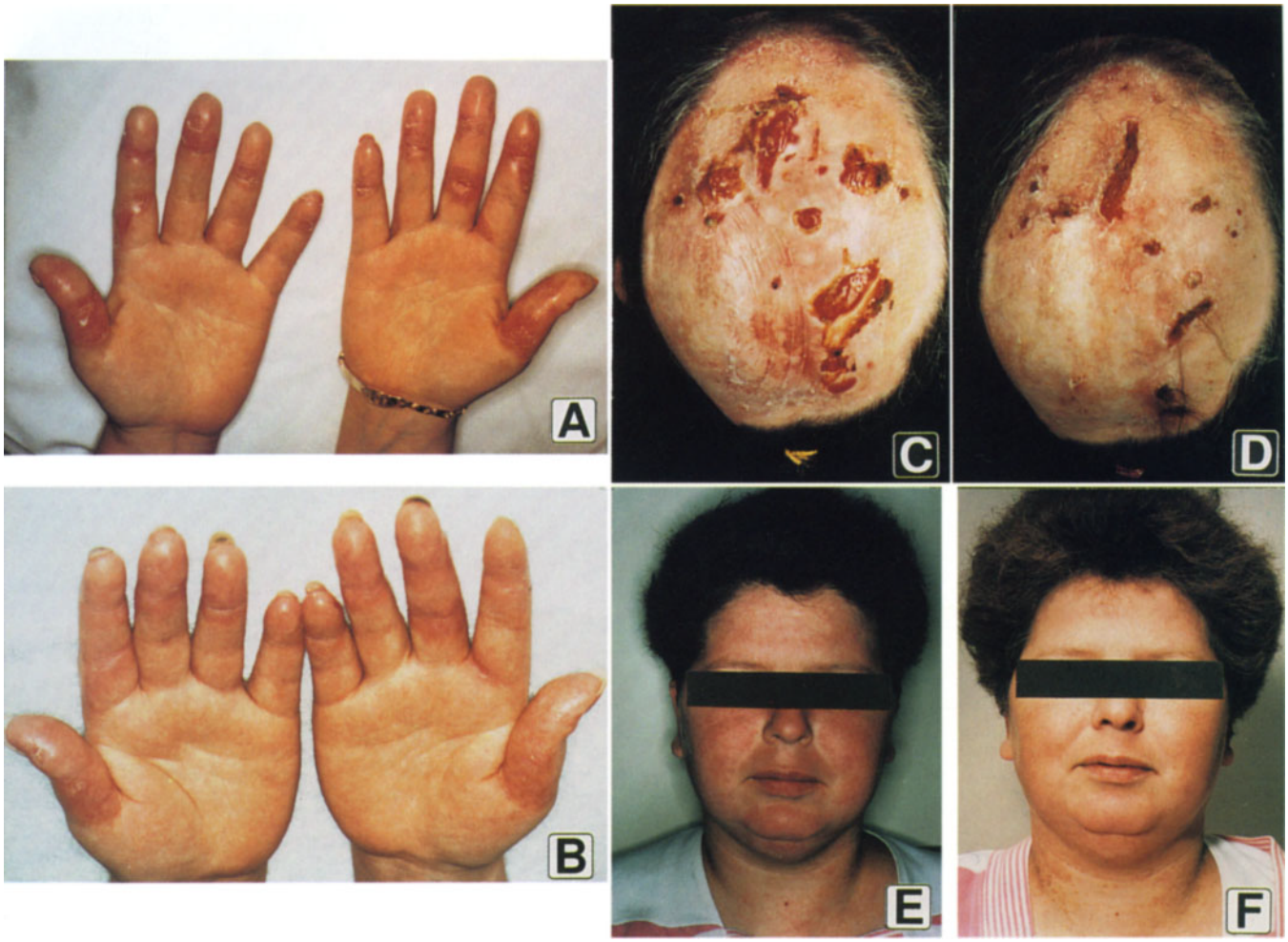

Figure 1. **A**, Patient 1 before cytarabine therapy. **B**, Patient 1 during cytarabine therapy. **C**, Patient 2 before cytarabine therapy. **D**, Patient 2 during cytarabine therapy. **E**, Patient 3 before cytarabine therapy. **F**, Patient 3 during cytarabine therapy.

sone and retinoids (1). In some patients, these medications have little effect, while in others, intolerable side effects may develop, indicating a need for additional therapeutic interventions. Cytarabine (cytosine arabinoside) is a cytidine analog with potent immunosuppressive properties (2) that has recently been used to treat rheumatoid arthritis (RA) (3). Furthermore, cytarabine can increase DNA methylation (4,5), and diminished T cell DNA methylation has been implicated in the pathogenesis of systemic lupus erythematosus (SLE) (6,7). These considerations prompted us to investigate the efficacy of cytarabine in patients with refractory cutaneous lupus.

We treated 3 female patients, using a protocol previously shown to be immunosuppressive in humans (8). Written consent was obtained from all patients. None of the patients had significant hematologic abnormalities or impairment of renal function, none were receiving other DNA synthesis inhibitors, and all were using effective contraception.

Cytarabine was administered subcutaneously at 2 mg/kg for 5 consecutive days, together with ondansetron orally 8 mg 3 times a day. This was repeated every fourth week for a total of 3 courses. Clinical assessment (Systemic Lupus Activity Measure) (9) and routine laboratory monitoring were performed weekly for the first cycle, then every other week for a total of 12 weeks.

Patient 1 is a 23-year-old woman who has had SLE for 17 years, manifested by a rash involving the face, hands, and upper trunk, photosensitivity, alopecia, oral/nasal ulcerations, arthritis, serositis, fatigue, Raynaud's phenomenon, leukopenia, hypocomplementemia, positive antinuclear antibodies (ANA), and positive autoantibodies to double-stranded DNA and Sm. She had previously been treated with hydroxychloroquine, chloroquine, quinacrine, prednisone, azathioprine, levamisole, methotrexate, cyclophosphamide, and nitrogen mustard. A combination of intravenous cyclophosphamide, prednisone (30 mg/day), and antimalarials resulted in mild improvement, but was complicated by retinal pigmentation, cataracts, and avascular necrosis. The other medications were either ineffective or poorly tolerated.

Cytarabine was administered at 2 mg/kg/day on weeks 1, 5, and 9. During the second week of each cycle, her rash began to clear, with maximum improvement during the third week (Figures 1A and B), and began to relapse during the fourth week. Improvement in fatigue, Raynaud's phenomenon, dyspnea, headache, and cortical dysfunction were also reported. Her C3 level normalized, and her C4 level rose from undetectable to borderline low. Therapy was accompanied by asymptomatic mild thrombocytopenia (147,000/mm^3) occurring during the second week. A mild leukopenia (3,100/mm^3) was observed on one occasion. Because the cutaneous improvement was not sustained, her prednisone dose was increased from 30 to 40 mg/day during the third course; however, this did not prolong the response.

Patient 2 is a 44-year-old woman who has had lupus for 15 years, manifested by photosensitivity, alopecia, discoid and ulcerative scalp lesions requiring skin grafts in 1988, arthritis, oral ulcerations, fatigue, serum positive for ANA, and autoantibodies to Ro. Treatment with prednisone, quinacrine, chloroquine, azathioprine, and hydroxychloroquine was previously ineffective. Cytarabine was administered as with Patient 1. Mild nausea and 1 episode of emesis accompanied the first course. Her scalp lesions began to improve by the second week, and improved slowly but continuously over the second course of therapy (Figures 1C and D). Improvement in arthritis was also noted. The dose of cytarabine was increased to 3 mg/kg/day for the third cycle in an attempt to improve the clinical response. This resulted in several episodes of emesis and a diffuse pruritic rash due either to the ondansetron or cytarabine, but neither thrombocytopenia nor leukopenia were present. No further increase in efficacy was observed at this dose, and the patient's scalp disease relapsed 4 weeks after the last cycle.

Patient 3 is a 35-year-old woman who has had subacute cutaneous lupus for 14 years, manifested by a nonscarring photosensitive rash, arthritis, oral and nasal ulcers, serositis, Raynaud's phenomenon, fever, fatigue, serum positive for ANA, and autoantibodies to Ro. Treatment with prednisone, azathioprine, quinacrine, hydroxychloroquine, dapsone, and sulfapyridine was either ineffective or poorly tolerated. Cytarabine was administered as above. Again, dramatic clearing of the skin lesions was observed during the second and third week of therapy (Figures 1E and F), with a tendency to relapse during the fourth week. Because of the transient improvement, her dose was increased to 3 mg/kg/day during the third cycle of therapy. This was complicated by thrombocytopenia (24,000/mm^3) and menorrhagia. The platelet count normalized within 1 week, but the increased dose did not result in prolonged skin improvement.

In these 3 cases, cytarabine caused a significant response in otherwise refractory cutaneous lupus. The improvement was rapid, but relapsed during the fourth week in 2 cases. Other disease manifestations also appeared to improve, suggesting that cytarabine might be effective for other SLE manifestations. Attempts to prolong the response with higher doses resulted in increased toxicity, with no apparent additional benefit. More frequent dosing, such as every 3 weeks, or possibly a lower dose given daily, would likely produce a more consistent response.

The major toxicities encountered were nausea, thrombocytopenia, and 1 allergic reaction. Thrombocytopenia was potentially the most serious complication, but this resolved rapidly, as observed earlier (3). Thrombocytopenia was most severe at 3 mg/kg of cytarabine. Since lower doses were equally effective, there should be no need to use higher doses in future studies. Leukopenia was also observed, but was mild and uncomplicated. The allergic reaction was a diffuse pruritic rash, which may represent an idiosyncratic reaction to 1 of the medications.

The clinical benefit observed may be due to cytarabine's known immunosuppressive effects. However, it is noteworthy that azathioprine and prednisone were not effective in these patients. This raises the possibility that additional properties unique to cytarabine, such as DNA hypermethylation, might contribute to its apparent increased efficacy. It would thus be important to serially measure T cell deoxymethylcytosine content. Unfortunately, the large amount of blood required for each determination (7) has precluded these studies. Nonetheless, the results support the hypothesis that immunosuppressives that hypermethylate DNA might be more effective than other immunosuppressives in the treatment of cutaneous lupus.

In summary, cytarabine appears to be an effective treatment for these 3 patients with otherwise refractory cutaneous lupus. Further studies appear to be justified.

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