Absence of fetal cell microchimerism in cutaneous lesions of lupus erythematosus

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Fetal cell microchimerism develops in all human pregnancies[1] and has been associated with autoimmune diseases such as systemic sclerosis.[2] It has been suggested that these disorders may be the consequence of an immune reaction between fetal and maternal cells in women after pregnancy. More recently, results from our laboratory suggest that microchimeric cells of fetal origin may differentiate into thyrocytes[3] or hepatocytes[4] in thyroid and liver specimens from women with non-autoimmune diseases. We therefore developed an alternative hypothesis suggesting that microchimeric stem cells may have the ability to participate in the maternal response to tissue injury.[5]

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women and can target multiple organ systems with severe life threatening complications. In some patients, however, lupus is limited to skin involvement, with discoid or subacute cutaneous lesions, and few of these patients develop severe disease.[6] Mosca *et al* recently reported that the number of microchimeric cells found in patients with lupus nephritis was higher than in lupus patients without nephritis.[7] Their results suggest that the severity of the disease may influence the level of fetal cell microchimerism.

METHODS AND RESULTS

To further investigate the relationship between fetal cell microchimerism and SLE, we examined biopsy specimens of affected skin from women with previous male pregnancies affected with lupus as well as other skin disorders for the presence of male microchimeric cells. Affected skin sections from six patients with lupus erythematosus (five cases of systemic and one case of cutaneous lupus) and four patients with dermatomyositis or mycosis fungoides (table 1), all with at least one male pregnancy, were analysed for the presence of microchimeric male cells by fluorescence in situ hybridisation (FISH) using probes specific for the X and Y chromosomes. Between three and six sections were examined from each subject and the scoring was blinded according to the diagnosis or the pregnancy history of the patients. No microchimeric male cells were detected in any tissue sections from these subjects. More than 90% of the nuclei had two detectable X chromosome signals (fig 1). We also examined skin sections from six women with no history of a male pregnancy; these sections also had no detectable male cells. Both X and Y chromosome signals were detected in >90% of nuclei from male control tissue.

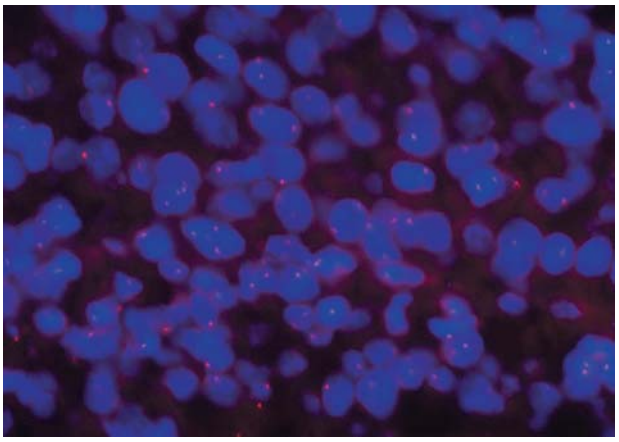

Figure 1 FISH analysis of epidermal keratinocytes. Two X chromosome signals (red) are detected in almost all cells at ×400 magnification. As all chromosome signals may not be in the same plane of focus, some cells appear to have only one X chromosome. No evidence of a Y chromosome signal (green) was found in any female tissue examined.

Table 1 Subject history and results of FISH analysis

Subject	Age	Diagnosis	Male pregnancy	Blood transfusion	Sections examined (n)	Male cells detected
1	61	SLE	Yes	Yes	5	No
2	36	CLE	Yes	No	5	No
3	42	SLE	Yes	No	3	No
4	50	SLE	Yes	No	3	No
5	41	SLE	Yes	No	5	No
6	34	SLE	Yes	Yes	5	No
7	74	DM	Yes	Yes	6	No
8	42	MF	Yes	No	4	No
9	59	MF	Yes	No	5	No
10	89	MF	Yes	No	5	No
11	35	SLE	No	No	5	No
12	49	DM	No	No	5	No
13	31	DM	No	No	5	No
14	27	MF	No	No	5	No
15	56	MF	No	No	4	No
16	26	MF	No	No	4	No

No patient had a history of a male twin or a solid organ transplant at the time of biopsy.
SLE, systemic lupus erythematosus; CLE, cutaneous lupus erythematosus; DM, dermatomyositis; MF, mycosis fungoides.

DISCUSSION

The results presented here support the findings of other studies that have reported the lack of an association between fetal cell microchimerism and SLE.[8 9] Recently, we reported the case of a woman with severe SLE and demonstrated the presence of large numbers of male cells, presumably of fetal origin, in necropsy specimens from her clinically affected tissues.[10] This patient had a severe vasculitis and ultimately died of intestinal necrosis and perforation. In contrast, all of the patients in the present study were alive, underwent skin biopsies, and had better prognoses than the case in our previously published report.

Possibly, the cases of cutaneous and moderate systemic lupus in the current study do not cross the threshold of disease severity to recruit microchimeric cells to areas of tissue damage. Therefore, the results of the present study combined with those of our previous case report support the findings by Mosca *et al* and suggest that extensive maternal tissue damage may be required for the development of microchimerism in cases of SLE.

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Diagnostic value of anti-cyclic citrullinated peptide antibodies to detect rheumatoid arthritis in patients with Sjögren's syndrome

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Sjögren's syndrome (SS), prevalence 3–4%,[1] is a chronic autoimmune disorder characteristically affecting the salivary and lachrymal glands. Rheumatoid arthritis (RA), prevalence 1–4%, is a chronic inflammatory autoimmune disease.[2]

The diagnosis of RA relies mainly on clinical manifestations and serological markers such as rheumatoid factors (RF). The sensitivity of RF in RA is 75% and the specificity 74%.[3] Furthermore, RF is positive in 40–70% of patients with primary SS.[4] Many patients with primary SS and chronic polyarthritis consequently have RF without ever developing RA. An enzyme linked immunosorbent assay (ELISA) test has been developed that recognises a cyclic variant of a citrullinated peptide (CCP).[2] The sensitivity of the first generation anti-CCP test in RA ranges from 41 to 68%,[5 6] the sensitivity of the second generation is 82%.[7] The specificity, however, is 96–98%.[3 5–7]

We analysed data from 164 patients who were diagnosed as SS according to the revised version of the European criteria.[8] These criteria allow a diagnosis of SS if at least four items out of six or three objective items are present. Unfortunately, no single laboratory test is sufficiently reliable to confirm a clinical diagnosis of SS.[9] Therefore, a second group was assembled with patients in whom three items were present and in whom no other disease could explain the sicca symptoms. This group is further referred to as Sjögren's-like syndrome.

The medical records from all patients were further investigated for RA, according to the 1987 revised criteria.[10] RF and anti-CCP antibodies were determined in the same serum samples using the ELISA anti-CCP mark 2 (second generation) kits from Immunoscan RA, Euro-Diagnostica AB (Arnhem, Netherlands) and the IgM RF ELISA test. All the data were analysed using the SPSS/PC software, version 11.0.

Table 1 shows that both groups were similar. Furthermore, it shows that anti-CCP has a high specificity (98.8%), in contrast with the low specificity of RF (60.6%).

The diagnostic value of the RF test in patients with SS is questionable because of its low specificity (60.6%) in such patients. In this study we found a specificity of 98.8% for anti-CCP in the SS population for RA. The major strength of these data is to emphasise the fact that anti-CCP is not present in patients with primary SS who do not have RA, in contrast with the high prevalence of RF in patients with primary SS.