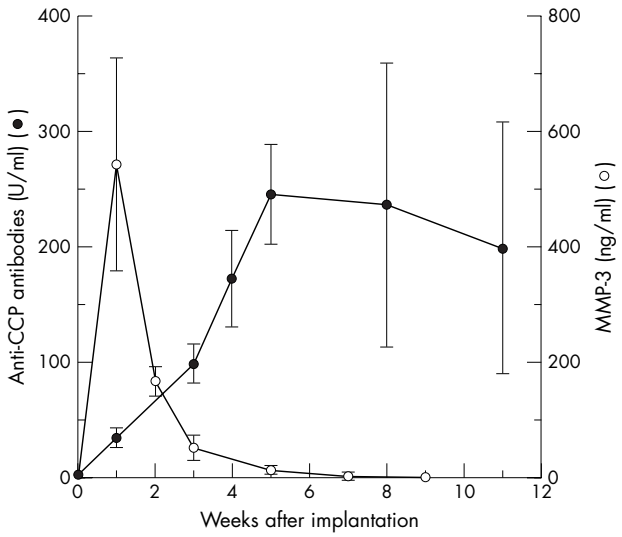

Figure 1 Time course of the serum levels of anti-CCP and MMP-3 in SCID-HuRAg mice. The results represent two independent experiments. The tissues from each of two patients were transferred to each of eight mice and each point represents a mean (SD) value (n = 8). Anti-CCP antibodies were measured with a second generation anti-CCP enzyme linked immunosorbent assay (ELISA) kit (Immunoscan RA the anti-CCP Mark2 kit; Euro-Diagnostica, Arnhem, The Netherlands). The concentrations of MMP-3 in sera were determined by a one step sandwich ELISA system using a human MMP-3 kit (Panaclear MMP-3; Daiichi Pure Chemicals Co, Tokyo, Japan). Both assays were conducted according to the manufacturer's instructions. Their cut off values in human serum levels are 25 U/ml for anti-CCP and 29.0 ng/ml for MMP-3. Non-implanted SCID mice sera were used as controls (week 0).

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This study was approved by the ethics committee of Hokkaido College of Pharmacy.

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Absence of anti-cyclic citrullinated peptide antibodies in erosive osteoarthritis: further serological evidence of the disease as a subset of osteoarthritis

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Erosive osteoarthritis (EOA) is considered to be a rare subset of osteoarthritis (OA) characterised by destructive changes involving the proximal interphalangeal and distal interphalangeal joints.[1–3] Laboratory findings are usually negative even though a slight increase of erythrocyte sedimentation rate may occur.[2 3] Radiologically, central erosions and the "gull wing" deformity characterise the disorder.[4] Synovial pathology shows changes consistent with both rheumatoid arthritis (RA) and OA.[1 2] Histological examination of synovium from patients with EOA joints shows lining cell hyperplasia, lymphocytic infiltration, and pannus formation, features indistinguishable from those of RA.[1]

The relationship between EOA and classical OA is controversial, as some authors consider it to be a separate disease entity, some regard it as one end of the spectrum of OA, and some regard it as an interface between OA and RA.[1 4] A relationship between EOA and RA was first suggested by Ehrlich,[5] who noted the superimposition of clinical, laboratory, and imaging findings of RA in 62 of 170 patients initially diagnosed with EOA. Moreover, in the early stages of the disease, the differential diagnosis between EOA and other arthritis, such as RA or psoriatic arthritis, may pose a challenge, requiring a number of laboratory tests and investigations.[3 6–8] It is well known that anti-cyclic citrullinated

Table 1 Characteristics of our patients and controls

	No	Age (years) Mean (SD)	Sex	Disease duration (years) Mean (SD)	IgM RF positive No (%)	IgG anti-CCP positive No (%)
EOA	32	59.3 (11.4)	26F; 6M	8.3 (3.6)	0	0
NOA	35	61.5 (9.2)	21F; 14M	9.1 (3.2)	0	0
RA	45	52 (16)	32F; 13M	10.6 (6.5)	28 (62)	31 (69)
Healthy subjects	50	54.4 (18.2)	39F; 11M	–	2 (4)	0

peptide antibodies (anti-CCP) are highly specific for RA and good predictors of radiographic joint damage[9]; for that reason this study aimed at detecting these autoantibodies in serum samples of patients with EOA, in order to ascertain their clinical usefulness and, possibly, to contribute to the clarification of the relationship of EOA with classical OA and RA. On the one hand, positive results may support the hypothesis that EOA is an interface between OA and RA, but, on the other hand, negative results may support the hypothesis that EOA is one end of the spectrum of OA.

We evaluated 32 patients with EOA showing typical EOA radiographic findings.[6] The control group included 35 patients affected by nodal OA of the hands (NOA) fulfilling American College of Rheumatology criteria[10] and 50 healthy subjects. All the patients were examined for exclusion of psoriatic arthritis, RA, undifferentiated spondyloarthropathies, gout, and pseudogout. In addition, 45 patients with RA were examined to test the sensitivity and specificity of our anti-CCP enzyme linked immunosorbent assay (ELISA) kit (table 1).

The second generation of anti-CCP antibodies was tested with an ELISA commercial kit (Axis-Shield, UK). All groups were assayed for IgM rheumatoid factor (RF), with ELISA methodology (Orgentec, Germany). Patients with EOA and the control group were negative for anti-CCP, whereas two healthy subjects were IgM RF positive. Of 45 patients with RA, 23 were positive for RF and anti-CCP, 5 for RF, 8 for anti-CCP, and 9 negative for both. The specificity of anti-CCP in diagnosing RA is well known,[9] and in our study it was 100%. For this reason the detection of anti-CCP has a higher diagnostic performance than RF, by virtue of its higher specificity. The sensitivity of anti-CCP was 69%, but becomes 80%, if calculated in conjunction with RF.

In our opinion, the absence of anti-CCP antibodies in EOA as opposed to their high prevalence in RA is a further difference between EOA and RA, supporting the hypothesis that EOA represents a subset of OA, as suggested by other authors.[2–4 7] Therefore, the anti-CCP assay can be considered a further useful test to help to discriminate between EOA and RA in the early stage of the disease. The conjunction of both a negative RF test and a negative anti-CCP test make the diagnosis of RA unlikely and argue for the diagnosis of EOA.

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Paternal and maternal exposure to leflunomide: pregnancy and neonatal outcome

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Leflunomide is a pyrimidine synthesis inhibitor with proven teratogenic and fetotoxic effects in animal studies, and its active metabolite is detectable in plasma up to 2 years after discontinuation of the drug.[1–3] For this reason the fetus could have in utero exposure to leflunomide up to 2 years after the end of treatment unless an oral cholestyramine regimen, 8 g three times daily for 11 days, is administered to obtain undetectable plasmatic levels.[1–3]