Case report

Rheumatoid polyarthritis after rubella

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SUMMARY A 24-year-old woman developed persistent polyarthritis indistinguishable from rheumatoid arthritis after rubella. The arthritis persisted for approximately 30 months and was associated with high levels of antibody to rubella virus and with rheumatoid factor. The antibody titres declined *pari passu* with clinical improvement which progressed to complete resolution. Fractionation of serial serum specimens showed a substantial and persistent IgM antibody response to rubella virus. Rubella antigen was not demonstrated in the synovial exudate.

The association of a transient, self-limiting, arthritis with natural rubella infection or following immunisation with attenuated rubella virus is well documented (e.g. Moylan-Jones and Penney, 1962; Kantor and Tanner, 1962; Chambers and Bywaters, 1963; Yanez *et al.*, 1966; Thompson *et al.*, 1971). Less commonly, the arthritis relapses (A. J. Tingle *et al.*, personal communication, 1977) or causes longer disability—'catchers crouch syndrome' (Spotswood *et al.*, 1977).

A causal connection between rubella virus infection and juvenile or adult rheumatoid arthritis (RA) has been sought by various workers during the past 20 years but with generally negative results (see Hart and Marmion, 1977). Nevertheless, the resolution of rubella virus infection appears to be protracted in some patients with RA. Thus, Ogra *et al.* (1975) postulated prolonged infection with rubella virus in some patients with juvenile RA on finding high and persistent serum levels of IgM and IgG rubella antibody and rubella antigen in smears of synovial fluid cells by immunofluorescence. Rubella virus has also been isolated from synovial fluid after natural infection (Hildebrandt and Maassab, 1966) and after immunisation with rubella vaccine (Weibel *et al.*, 1969). In another report by Ogra and Herd (1971), rubella virus was isolated from the synovial fluid of 3 previously healthy children 3-4 months after

immunisation. Those authors also described a child with a pre-existing chronic polyarthritis who developed repeated episodes of joint effusion for 3 months after immunisation but without virus isolation.

In adults there have been occasional reports suggesting progression of rubella arthritis to typical RA. Martenis *et al.* (1968) describe one patient in detail and mention another less adequately documented case (Riddell, 1962). Perhaps the immunological abnormalities that characterise RA may be precipitated, or accentuated, in some patients by a rubella virus infection, but the infrequent association observed between rubella infection and RA may be more of a chance inter-relating event than true cause and effect.

Because of these associations, we describe the case of a 24-year-old woman who had an illness resembling rubella and subsequently developed an RA-like condition with positive latex and sheep cell agglutination tests and a raised erythrocyte sedimentation rate (ESR). This state lasted for more than 24 months and was accompanied by high levels of antibody to rubella virus. Then her polyarthritis resolved in step with a fall in antibody levels against rubella virus, particularly in the IgM fraction.

Case history

A 24-year-old woman, previously healthy, developed a sore throat and coryza in mid-June 1970. Two days later an itchy, erythematous rash appeared on her

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arms, legs, and trunk. 3 days later she developed a flitting monarthritis. The affected joints were painful, obviously swollen and inflamed, and the attacks lasted several hours. There was no morning stiffness. Tetracycline, penicillin, and cotrimoxazole were given in turn but were discontinued because of side effects.

The flitting joint symptoms and the rash persisted; the latter was variable in severity, becoming more evident towards evening. On July 9th she was referred to hospital where a provisional diagnosis of rheumatic fever was made. A throat swab yielded scanty β -haemolytic streptococci but the antistreptolysin O titre was less than 125 Todd units; the RA latex test was negative but her ESR was 40 mm/h. Radiographs of the chest, hands, and wrists showed no abnormality.

On admission to hospital on July 23 she was pyrexial (temperature up to 39.2°C) with a variable rash on her back, arms, and legs. Posterior cervical lymph nodes were enlarged, there was a small corneal ulcer with marked conjunctivitis in the left eye; there was also a monilial infection of the vulva. Several joints were painful on movement, although not swollen.

Electrocardiogram, chest x-ray, urinalysis, and routine biochemical tests showed no abnormality but the ESR had increased to 123 mm/h. The RA latex fixation and antinuclear factor (ANF) tests were negative and LE cells were not demonstrated. Serological tests for brucellosis, infectious mononucleosis, and syphilis were negative. Rubella was

suspected although there was no known contact; a serum sample taken on July 24—6 weeks after the onset of sore throat and rash—was eventually reported to have a haemagglutination inhibition (HAI) titre of 1/512 and a CF titre of 1/32. Her pyrexia and joint symptoms settled with soluble aspirin and the corneal ulcer and monilial infection responded to local treatment. On discharge from hospital on 18 August 1970, there was no arthritis or fever but there was still some rash on her limbs.

On review as an outpatient in November 1970 she stated that she felt very well. Her hands showed the clinical appearance of RA with swelling of the proximal interphalangeal joints but radiographs showed no abnormality. Haemoglobin was 11.4 g/dl and the ESR was normal at 12 mm/h. The RA latex and ANF tests were again negative.

On February 2, 1971 she was readmitted to the same hospital with a recurrence of polyarthritis after an upper respiratory tract infection in December 1970. Her haemoglobin had fallen to 7.0 g/dl and the ESR was considerably raised at 110 mm/h. Her condition did not improve and she was transferred on March 11 to the Rheumatic Diseases Unit, Northern General Hospital, Edinburgh, for further investigation and treatment.

On examination there was spindling and cyanosis of the proximal interphalangeal joints and some swelling of the metacarpophalangeal joints in both hands (Fig. 1). The wrists were slightly swollen, there was some limitation of extension in the elbows and synovial swelling and effusions in both knees

Fig. 1 Polyarthritic changes in the patient's hands, March 1971.

The ankles were also slightly swollen. Radiographs of the hands and wrists showed some periarticular osteoporosis but no erosions. The knees and feet were radiographically normal. A few cervical lymph nodes were palpable but there was no rash.

Haemoglobin was 8.5 g/dl and ESR was 132 mm/h. The anaemia was haemolytic in type and her serum contained a weak haemagglutinin detectable with enzyme-treated cells, and at all temperatures. The Rose-Waaler test (SSCT) was positive at 1 in 128 on March 11 but the tests for ANF and LE cells were again negative. Rubella antibody tests on March 12 and April 16 gave HAI titres of 1/1024–2048 and CF titres of 1/16.

The joint symptoms settled down with bed rest, splinting, ACTH 20 units daily, and full doses of soluble aspirin. The left knee was aspirated on two occasions and injected with hydrocortisone. The synovial fluid contained 12 500–16 000 cells/ml which were predominantly mononuclear. The anaemia was corrected by 2 g intravenous iron and by transfusion of 4 units of packed cells. On discharge on May 15 she was feeling quite well and had only minimal discomfort in her joints.

On review at outpatient department in July 1971, her haemoglobin had fallen to 7.1 g/dl and the ESR was 104 mm/h. Her joint pain and stiffness had returned with large effusions in both knees. She was therefore readmitted on July 18 and received a further transfusion of packed cells and started treatment with rifampicin 600 mg daily. She was discharged on the 23rd without further treatment but was seen regularly as an outpatient thereafter.

During the following 16 months she continued to complain of variable joint pain and stiffness. Moderate to severe anaemia persisted despite oral iron, and the ESR remained raised. After 6 months of continuous therapy without obvious benefit, rifampicin was withdrawn in February 1972. Recurrent effusions in her knees were aspirated on six occasions between September 1971 and June 1972. Mononuclear cells were less predominant in these samples of synovial fluid than in the specimens obtained initially in May 1971, and 30–55% polymorphonuclear leucocytes were seen. In cytospins of synovial fluid cells intracellular inclusions of IgG and IgM were demonstrated by immunofluorescence.

By November 1972 the haemoglobin had increased to 14.4 g/dl, the ESR had fallen to 4 mm/h, and the serological tests for rheumatoid factor were negative. She felt very well and her joints appeared normal apart from a small effusion in the left knee. By March 1973 she was symptom-free and all signs of arthritis had disappeared. When seen in December 1973 she was 4 months pregnant and had no joint symptoms. A healthy baby (her second child) was delivered in May 1974, without any post-partum recurrence of her joint symptoms. She was last seen on January 19, 1977 when she stated that she had been well until 3 months previously when she had had a transient recurrence of pain and swelling in her right knee which her general practitioner had attributed to a 'housemaid's knee'. This settled down with a supporting bandage and has not troubled her since then. There were no residual signs of arthritis in any of her joints (Fig. 2) and radiographs showed

Fig. 2 The patient's hands, January 1977.

no abnormality in her hands, wrists, knees, and feet. Tests for rheumatoid factor and antinuclear factor were negative, haemoglobin and ESR were normal, and the rubella HAI and CF titres were 128 and 32 respectively. The course of the illness and serological findings are summarised in Fig. 3.

VIROLOGICAL INVESTIGATIONS

Tests for rubella antigens in synovial fluid cells

Specimens of synovial fluid from the knees obtained on September 8, 1971, January 4 and June 28, 1972 were examined for rubella antigen by binding of fluorescein-labelled and radiolabelled antirubella antibody. A concentrated IgG fraction (rubella HAI titre 1/512) was prepared by DEAE-cellulose chromatography from a sample of the patient's serum obtained on October 6, 1971. Aliquots were labelled with fluorescein isothiocyanate by the dialysis method (Clark and Shepard, 1963) and with ^{125}I by the iodine monochloride method (McFarlane, 1958).

The first two samples of synovial fluid were maintained in Eagle's medium/10% fetal calf serum in Leighton tubes for 33 and 20 days respectively. The 'flying' coverslips were then removed, fixed in cold acetone, and incubated with fluorescent or radiolabelled IgG antirubella antibody but no specific binding was observed. (These two samples of synovial fluid, and others taken early in the illness, were subsequently lost by refrigerator failure and were not available for attempted isolation of virus.)

The third specimen of synovial fluid (28/6/72) was examined before culture. Suspensions of washed synovial cells were incubated with both reagents at 4°C. Acetone-fixed cytosmears of fresh cells were also incubated with the FITC-labelled antirubella IgG but no specific binding was demonstrated in either system.

Attempted isolation of rubella from synovial fluid

Synovial fluid (23/8/72) for culture was taken at the time of persisting rubella IgM in patient's serum and

Fig. 3 Rubella antibody and viral studies in relation to other laboratory investigations and the general clinical picture in the patient aged 24.

contained substantial amounts of rubella antibody (see serological section). Two virus isolation methods were used.

(a) *In rabbits*: The method followed that of Kono *et al.* (1969) for inoculation of pregnant rabbits with strains of rubella. Two synovial fluid specimens, both collected on August 23, 1972, previously stored in liquid nitrogen, (i) in Eagle's medium containing 10% DMSO, and (ii) as concentrated synovial fluid cells, were inoculated into ear veins of two pregnant rabbits on day 8 after the copulation. The rabbit littered 22 days later and the 10 neonates showed no signs of congenital rubella including eye changes. All neonates died within 2 days of birth; rubella virus was not isolated from their heart, liver, or brain. The rubella HAI titres in the mothers remained negative at <16 .

(b) *In tissue culture*: The synovial cells stored in DMSO were fused with RK₁₃ and Vero cells using UV-inactivated Sendai virus (Watkins, 1971) in efforts to circumvent the possible neutralising effect of rubella antibody in the fluid. Fused and control cells were split once a fortnight and observed for 2 months. At fortnightly intervals fused Vero cells were tested by immunofluorescence with rubella antiserum and antirabbit Ig-FITC as described previously (Hart and Marmion, 1977). No rubella antigens were seen in Vero cells and no cytopathic effect was detected in RK₁₃.

Rubella antibody in the patient's serum and synovial fluid

Sera. 19 samples of serum collected over a period of 68 months were available. 10 of these samples, obtained between May 1971 and February 1972, were fractionated under acidic conditions by gel filtration on Sephadex G200 columns.

Fractionation of sera by gel filtration. In initial runs, 3 ml serum were applied to Sephadex G200 columns (40 × 3 cm) equilibrated in Tris/HCl buffer (0.05 mol/l, pH 8.0). 4.0 ml fractions were collected and the optical density was recorded at 280 nm. The excluded peak 1 fractions were pooled and concentrated to approximately the original serum volume by ultrafiltration in Centrifo membrane filters (Amicon). Preliminary examination of the concentrated peak 1 fractions apparently showed IgM antibody in the rubella HAI system. However, when the fractions were subjected to immunodiffusion analysis with monospecific anti-IgM and anti-IgG antisera, significant contamination with IgG was found; presumably because of complex formation between IgM rheumatoid factor and IgG.

To overcome this problem all subsequent fractionations were carried out at pH 4.0 in glycine/HCl buffer. The individual fractions from the ascending

limb of the excluded first peak were pooled, the pH was adjusted to 7.0 with 0.1 M NaOH, and the pool was concentrated by ultrafiltration. Bovine serum albumin was added to a final concentration of 1.00 to reduce denaturation of IgM. These fractions were shown to be free of IgG by immunodiffusion analysis. To check that separation of IgM from IgG was complete, IgG prepared from the patient's serum by fractionation on DEAE-cellulose (DE 52) was labelled with ¹²⁵I by the iodine monochloride technique, and added to the serum before fractionation. On the 4 occasions when this additional safeguard was employed (sera 3, 4, 6, & 11), the fractions in the ascending limb of the first peak were shown to be free of IgG by absence of radioactivity as well as by immunodiffusion.

The results are given in the Table; rubella HAI activity was found in the majority of the IgM fractions prepared in this way. In addition, rheumatoid factor was detected by the tube latex test at a titre of 1/5120 or greater in the IgM fraction of 4 sera tested (1, 4, 7, & 10).

The results of less satisfactory separations of IgM and IgG rubella antibody on sucrose density gradients, utilising sera taken later in 1972 and in 1973, indicate a slow fall in IgM levels (Table).

Synovial fluid. Only one specimen of synovial fluid, obtained on August 23, 1972, was tested for rubella HAI antibody and had an antibody titre of 1/512. By an indirect immunofluorescence system using BHK₂₁ cells infected with rubella virus (Hart and Marmion, 1977) and an anti-IgM conjugate rubella, IgM antibody appeared to be present in this synovial fluid. However, it is known that rheumatoid factor will react with specifically bound IgG antibody in immunofluorescence systems (McCormick, 1962) and it has also been suggested that the presence of rheumatoid factor will interfere with the detection of IgM antibody to virus antigens (Shirodaria *et al.*, 1973).

OTHER INVESTIGATIONS

Lymphocyte function tests

Lymphocytes separated on a Triosil/Ficoll gradient from blood obtained on January 19, 1977 showed a normal response to phytohaemagglutinin and pokeweed mitogen. There was virtually no response to PPD or Candida antigen. No information is available on lymphocyte function during the course of her illness.

HLA phenotype: A9; B13-W40.

Discussion

The clinical picture at the onset of the illness—sore throat, enlarged cervical lymph nodes, erythematous

Table Rubella HAI titres on whole serum and IgM fractions prepared on Sephadex G200 at pH 4.0 and on sucrose gradients

Serum no.	Date	Whole serum				IgM fractions separated on Sephadex G200 at pH 4.0		IgM fractions prepared on sucrose gradients: rubella HAI titre
		Rubella		SSCT	Latex	Rubella HAI titre	Tube latex titre	
		HAI	CF					
1	13/ 5/71	512	32	512	>5120	2	5120	4
2	26/ 6/71	2048	..	512	>5120	—	—	—
3	14/ 7/71	2048	..	256	>5120	128*	—	—
4	22/ 7/71	2048	32	..	..	64*	5120	—
5	8/ 9/71	1024	..	128	..	2	—	—
6	6/10/71	2048	64	..	..	32*	—	8
7	3/11/71	2048	..	1024	>5120	4	5120	—
8	17/12/71	1024	64	..	..	64	—	—
9	4/ 1/72	2048	..	64	5120	64	—	—
10	24/ 1/72	..	..	—	..	64	5120	—
11	23/ 2/72	..	..	32	..	64*	—	—
12	26/ 4/72	1024	..	16	<20	—	—	8
13	23/ 8/72	1024	..	..	..	—	—	4
14	7/ 3/73	64	..	64	..	—	—	<2
15	6/ 6/73	16	..	256	..	—	—	<2
16	15/12/73	256	32	32	..	—	—	—
17	3/ 7/74	..	..	<16	<20	—	—	<2
18	15/ 1/75	..	..	<16	<20	—	—	—
19	19/ 1/77	128	32	<16	<20	—	—	—

— = not done; * ¹²⁵I-IgG added before fractionation but not detected in IgM fraction.

rash, monarthritis, and corneal ulceration—suggested a rubella infection. The finding of rubella antibody and an HAI titre of 512, and a CF titre of 32 six weeks after onset is good supporting evidence but virus isolation would have been better.

After the original febrile illness the subsequent course was clinically indistinguishable from active RA, as were the persistently positive tests for rheumatoid factor. It is therefore interesting that the patient recovered completely after 30 months, without clinical or radiographic residua. Systemic lupus erythematosus, rather than RA, seems unlikely in view of the persistently negative ANF tests. It is notable that during the period of the greatest clinical severity of the disease—with multiple joint pain and stiffness, synovial swelling and effusion—she had high antibody titres to rubella virus. It is also of interest that when she started to recover, and her joint symptoms and anaemia regressed and her erythrocyte sedimentation rate fell, the antibody titre to rubella virus declined *pari passu*.

Several authors (e.g., Haire and Hadden, 1970) have suggested that a persistent IgM antibody response to rubella virus, either in the congenitally infected infant or in young persons or adults, may indicate a continuing viral infection, perhaps with some concurrent viral immunosuppression. The results with our patient indicate a persisting rubella antibody response in the IgM fractions at least during the first 2½ years after the (presumptive) attack of rubella. The persistence of complement-

fixing antibody at 1/64 until December 1971 (i.e. 18 months after the onset of illness) also favours a persistent rubella infection. Failure to isolate or detect virus in the synovial fluid does not necessarily exclude its persistence in other cells or compartments of the joint cavity. London *et al.* (1970) have shown that in neonatally infected rabbits, rubella virus is found in highest concentrations in chondrocytes, but cartilage was not examined in this case.

The persistence of positive tests for rheumatoid factor for at least 18 months after the original illness also suggests continuing antigenic stimulation, perhaps by chronic rubella virus infection. Transiently positive tests for rheumatoid factor can occur after uncomplicated rubella infection but are generally infrequent. Kantor and Tanner (1962) found negative tests for rheumatoid factor in all 14 of their patients with rubella arthritis followed for up to 5 years. In their series of 5 patients with rubella arthritis, Chambers and Bywaters (1963) found a positive latex test in only one and the SSCT (DAT) was negative in all. However, Yanez *et al.* (1966) describe one patient in whom a tube latex titre of 1/5120 persisted for 16 months after the original rubella infection although the rubella arthritis had subsided within 2 weeks. Johnson and Hall (1958) reported positive rheumatoid factor tests in 9/10 patients with rubella arthritis but in only 2/7 patients with rubella uncomplicated by arthritis.

Broadly speaking, the findings in this patient could be interpreted in one of two ways. Either the rubella virus infection was the direct cause of the RA-like

illness, achieving its persistence by viral immunosuppression, or the abnormal response to the rubella virus infection uncovered or precipitated an inherent defect of T lymphocyte regulation of B cells, manifesting as an episode of rheumatoid arthritis with a prolonged IgM response to rubella virus but with eventual restoration of control. The evidence is inadequate to decide between these alternatives. Lymphocyte function as judged by phytohaemagglutination and pokeweed stimulation was normal after the patient had made a complete recovery but we do not know if this was so during the acute phase of illness. It may be significant however that there was no lymphocyte stimulation by candida antigen although the patient had had a candida infection of the vulva before and during the early stages of her illness, perhaps implying at least some defect in her cellular immune response. It will be important to follow the patient over several years to ascertain if there is a return of the RA-like illness without an antecedent virus infection.

Surveys of HLA antigens in congenital rubella (Honeyman *et al.*, 1975) suggest that the presence of A1, or a combination of A1 and 8, favours rubella virus infection. However, our patient lacked both A1 and A8 and genetic predisposition to persistent rubella infection cannot be inferred on these grounds.

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