A case of Mollaret’s meningitis associated with a lymphoma

I. M. SWITHINBANK
B.A., M.B., B.Chir., M.R.C.P.

M. O. RAKE
B.Sc., M.B., M.R.C.P.

Kent and Canterbury Hospital, Canterbury CT1 3NG

Summary
A patient with recurrent benign meningitis (Mollaret’s meningitis) responding to treatment with colchicine by a reduction in frequency of attacks who has subsequently developed a non-Hodgkin’s lymphoma is described.

Introduction
Recurrent attacks of benign meningitis, first described by Mollaret (1945) are rare. Since then, a number of case reports have appeared (George and Westphal, 1965; Iivanainen, 1973; Nordbring and Gertzein, 1971). Reviews by Hermans, Goldstein and Wellman (1972) and Bruyn, Straathof and Raymakers (1962) list twenty well documented cases in the world literature.

Mollaret’s meningitis consists of intermittent attacks of acute meningitis. Symptoms of general ill-health and diffuse myalgia progress to development of a fever (up to 39°C) and signs and symptoms of acute meningitis. There may be some depression of conscious level, but focal neurological signs are rare. An attack lasts about 5 days. Recovery is complete with no neurological sequelae. CSF cell count shows an increase in polymorphs, lymphocytes and large, fragile, mononuclear cells (endothelial cells). CSF protein is raised, glucose is normal. All attempts to culture a pathogen have been in vain. The CSF returns to normal in parallel with the clinical syndrome.

Case history
A 63-year-old male retired office worker presented in January 1973 with a 1-year history of recurrent bouts of fever, sweating and severe headaches. There had been seven attacks at irregular intervals of between 1 and 3 months.

Apart from a short febrile illness whilst in Dunedin, New Zealand, in February 1971 as part of a world tour, there was no other relevant medical or family history.

The attacks started with a diffuse erythematous-urticarial rash mainly on the trunk and legs followed by a feeling of general malaise with development of fever (39–40°C) and sweating. During the ensuing 24–30 hr, headache gradually increased with photophobia in severe attacks. Confusion and disorientation also occurred and meningism developed. Over the next 4–5 days the symptoms subsided, the patient returned to normal and remained perfectly well until the next attack.

Examination both during and between attacks showed no abnormality apart from the severe meningism during an attack which disappeared within 3–4 days. Investigations showed that during attacks there was a rise in peripheral WBC to 15-0 x 10⁹/l with 88% polymorphs, 11% lymphocytes and 1% monocytes. No rise in eosinophil count was noted. A rise in ESR to 47 mm in the first hour also occurred. No abnormalities were detected in liver or renal function. Cerebrospinal fluid examination was performed and has been repeated both during and in between attacks (Table 1).

Culture of CSF, blood, urine, sputum, faeces, bone marrow and lymph node showed no growth of bacteria, fungi or viruses. Leptospira complement fixation test and Toxoplasma dye test were negative. Serology for fungal and viral antibodies showed no rises in titre.

X-rays of skull, sinuses and lumbar spine showed no abnormalities. Brain scan and RISA* cisternogram were normal. Air encephalogram showed moderate dilatation of the lateral ventricles, otherwise no abnormality. EEG (not during an attack) showed a diffuse, mainly posterior, bitemporal dysrhythmia of minor nature. Bone marrow biopsy was normal.

Serum was negative for auto-antibodies and anti-nuclear factor. DNA binding was less than 5%. Heaf test was positive. Kveim test was negative. There was no excess of urinary VMA or 5-HIAA.

The patient’s immunological competence was investigated and found to be normal, except for a slightly raised IgG and a very high serum IgE level. CSF immunoglobulins were within normal limits between and during attacks. During an attack C₃ was elevated to 1.95 g/l (normal 0.5–1.6). There was no excess conversion of complement or complex

* Radio-active iodinated serum albumin.

Requests for offprints: Dr M. O. Rake, B.Sc., M.B., M.R.C.P., Consultant Physician, Kent and Canterbury Hospital, Canterbury, Kent, CT1 3NG.

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initiated activity. Nitro-blue tetrazolium (NBT) testing, performed on blood and CSF between and during attacks, showed no abnormality.

Attacks continued during 1973/74 unaltered by treatment (Table 1).

On 8th January 1975 a trial of colchicine was started at a dose of 0·5 mg twice/day, later increasing to 0·5 mg thrice/day. There was a dramatic reduction in the frequency of attacks (Fig. 1).

In July 1975 an enlarged left supraclavicular lymph node was palpated. In January 1976 enlarged axillary and inguinal nodes were also demonstrated. A biopsy of the supraclavicular node showed excessive lymphocytic proliferation and fibrosis not diagnostic of inflammation or neoplasia. No treatment was given and the lymphadenopathy had almost completely subsided by June 1976.

By January 1977 glands were again palpable in the left supraclavicular fossa, axilla and groin. There was no hepatosplenomegaly. Repeat biopsy of a supraclavicular node showed histology similar to before, but appeared more likely to be lymphomatous on this occasion (Fig. 2).

Chest X-ray and hilar tomography showed right hilar gland enlargement. Intravenous urogram was normal. Bilateral pedal lymphangiogram showed pathologically enlarged lymph nodes in the left inguinal and left iliac areas. There were probable abnormal nodes in the right iliac area. The para-aortic nodes were equivocal. 99Tc sulphur colloid liver/spleen scan showed a normal liver outline with a low overall count-rate suggestive of diffuse liver disease. Bone marrow (iliac spine biopsy) (Fig. 3) showed heavy diffuse infiltration with lymphocytes and lymphoblasts. There was a pronounced fine reticulin network. Sternberg–Reed cells were not seen; there was no excess of plasma cells. The picture was that of a non-Hodgkin's lymphoma (Stage IVa).
carial skin rash has been reported in one previous case of Mollaret's meningitis (George and Westphal, 1965). This case also showed other systemic symptoms and the authors commented that she represented a combination of the features of familial Mediterranean fever (FMF) and Mollaret's meningitis.

Attacks of Mollaret's meningitis are unpredictable. Many cases have been reported in which attacks spontaneously ceased after many years. This makes assessment of a treatment of one patient difficult. A trial of colchicine was started (Gledhill et al., 1975) following reports of its success in reducing the frequency of attacks of FMF (Zemer et al., 1974; Dinarello et al., 1974). The mode of action is unknown. Colchicine is a spindle poison – inhibiting mitosis at metaphase (Inone, 1959). It has also been shown to interfere with polymorph function in vitro (Malawista and Bodel, 1967; Rajan, 1966). This could explain the inhibition of recurrent attacks of inflammation in FMF and Mollaret's meningitis.

During colchicine therapy the patient developed a non-Hodgkin's lymphoma. The pathogenesis of this is uncertain: it may be co-incidental, or it may be related to colchicine therapy. Although colchicine is known to produce chromosomal abnormalities (Ferreira, Buoniconti and Frota-Pessoa, 1973), the development of malignant disease in patients on long-term colchicine has not been described.

The development of a lymphoma may be a complication of Mollaret's meningitis – possibly analogous to amyloid in FMF. Alternatively, if the lymphoma is regarded as the primary condition, then the meningitis may be a secondary phenomenon. This is similar to the recurrent fever which is a well described (but rare) feature of Hodgkin's disease and other lymphomas (Reimann, 1977).

Mollaret's meningitis remains a disease whose cause is unknown. It does not appear to be inherited. There are similarities and overlapping of symptoms with FMF. Both respond to colchicine prophylaxis. The occurrence of recurrent febrile episodes is a common factor between Mollaret's meningitis, FMF and some lymphomas. All are diseases of unknown pathogenesis which may be linked by some abnormality of the immunological system.

Discussion

This case demonstrates the essential features of Mollaret's meningitis – recurrent meningitis, with complete recovery between attacks. Apart from confusion during attacks, there were no neurological signs. Involvement of other organ systems was confined to the occurrence of a skin rash during most attacks. Attacks occurred irregularly and continued with considerable frequency for three years until colchicine was started. The frequency of attack was reduced, increasing again on stopping colchicine temporarily (the disease was complicated by the development of a non-Hodgkin's lymphoma).

The signs and symptoms of Mollaret's meningitis are usually confined to the central nervous system (Hermans et al., 1972). The occurrence of an urti-

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**References**


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