Fatal varicella zoster infection in a severe steroid dependent asthmatic patient receiving methotrexate

A H Morice, W K Lai

Abstract

A case is described of fatal haemorrhagic varicella zoster in a steroid dependent asthmatic patient concurrently receiving methotrexate. The future management of patients on immunosuppressive steroid sparing drugs is discussed.

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Keywords: asthma, varicella zoster, immunosuppression.

A 33 year old steroid dependent asthmatic man presented with a three day history of lower chest epigastric pain with intermittent radiation through to the back. He had been maintained on systemic steroids for the past 14 years (prednisolone 2.5-20 mg/day or triamcinolone 40-80 mg intramuscularly at 4-6 week intervals). Three years before presentation he had been started on methotrexate at a dose of 15 mg/week which had led to an improvement in his asthma and allowed his maintenance dose of prednisolone to be decreased. There was no biochemical or haematological evidence of an adverse reaction at the bimonthly follow up visits. Whilst on methotrexate his usual maintenance dose of prednisolone was 7.5-12.5 mg/day. In the year before admission he had required five booster courses of prednisolone, and in the two days before admission he had increased the dose of prednisolone to 50 mg/day and continued on theophylline 1.2 g/day with bronchodilators and steroid inhalers. On direct questioning the patient stated that five weeks earlier his daughter had developed chickenpox and that he had had the illness as a child.

On examination he was afebrile, cushingoid, and had obvious pain. He had a scaly, erythematous, macular papular rash, mainly in the skin creases (groins, axilla, and neck) resulting from a chronic tinea infection which was noted to have increased in severity. He was otherwise normal apart from a tachycardia of 100 beats/min.

Investigations revealed a raised white cell count of $13.3 \times 10^9/l$ (neutrophils 11.65, lymphocytes 0.94, monocytes 0.61, eosinophils 0.04, basophils $0.05 \times 10^9/l$) and a platelet count of $205 \times 10^9/l$. The transaminase levels were raised (AST 208 U/l, ALT 157 U/l), but the serum amylase level was normal. The chest radiograph, abdominal radiograph, and ultra-

sound scan were unhelpful. The pain persisted and, following the development of pyrexia, he was started on intravenous cefuroxime 750 mg three times a day.

On the third day a non-itchy vesicular rash was evident mainly on the trunk and skin creases. Some of the vesicular lesions were necrotic and haemorrhagic. Immunofluorescence of fluid aspirated from the vesicles was positive for varicella zoster and acyclovir was started at 10 mg/kg intravenously eight hourly. A clotting screen was markedly abnormal with a KCCT of >200 seconds (normal 26-37), thrombin time of >60 seconds (control 12), prothrombin time of 48.4 seconds (control 12-15), and a fibrinogen level of <0.1 g/l (normal 1.6-3.9). Indeed, no coagulation was seen with conventional assays. The platelet count was $63 \times 10^9/l$. Disseminated intravascular coagulation was diagnosed and, despite intensive support, he arrested and died four hours later. Necropsic examinations revealed foci of haemorrhagic necrosis in the pancreas and liver. The varicella zoster antibody screen was negative, proving that this was disseminated varicella zoster infection and not disseminated zoster.

Discussion

Our patient developed haemorrhagic varicella zoster with subsequent rapidly fatal disseminated intravascular coagulation. There are approximately 200 000 cases of chickenpox each year in England and Wales leading to 1000 admissions and 20 deaths.¹ Most of the deaths occur in adults and one third of these patients are receiving immunosuppressive treatment.² A study of immunosuppressed children with malignancy has shown that the risk of disseminated varicella is six times higher, and that of death 17 times higher, than in normal children.³

The degree to which treatment with corticosteroids is a risk factor is difficult to determine. The Committee on Safety of Medicines has recently recommended that all patients taking systemic corticosteroids for purposes other than replacement should be regarded as at risk unless there is a history of previous chickenpox.² The Joint Committee on Vaccination and Immunisation has recommended that immunosuppressed patients who have been receiving steroids at a dose of 2 mg/kg/day for more than a week within three months of direct contact with chickenpox should be passively immunised with varicella zoster immunoglobulin if they do not already have antibodies to varicella zoster.⁴

In addition to long term oral steroids our patient was receiving methotrexate to minimise the side effects of the corticosteroid. Similar dual immunosuppression has previously been associated with fatal disseminated varicella zoster infection and it seems likely that patients taking combined therapy are at even greater risk.⁵

Our delay in diagnosis was partly attributed to the previous incorrect history of chickenpox, the long period between exposure and the onset

Department of
Medicine and
Pharmacology,
University of Sheffield,
Royal Hallamshire
Hospital, Sheffield,
S10 2JF, UK
A H Morice
W K Lai

Correspondence to:
Dr A H Morice.

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of symptoms, and the late onset of the vesicular rash. As a result of our experience in this case we recommend that varicella zoster antibodies should be measured in all patients receiving methotrexate and, if the result is negative, patients should be advised to seek medical attention when there is contact with chickenpox so that passive immunisation with varicella zoster immunoglobulins can be given.

Active immunisation with varicella vaccine is available at present in the UK on a named patient basis. Trials with the vaccine have been performed in healthy adults and in healthy children and those suffering from leukaemia. More than 95% of healthy children seroconvert following vaccination, and more than 90% are fully protected on subsequent exposure to the virus. In children with leukaemia two doses were required to induce seroconversion in 90%, with a protection rate of 85%. In healthy adults seroconversion was harder to achieve and there was a lower protection rate of 70%.⁶⁷ Pro-

tection of immunosuppressed adults may therefore be harder to achieve and, at present, active vaccination cannot be recommended. Increased awareness, prevention of exposure, passive immunisation, and antiviral therapy are all required in the management of this complication of immunosuppression.

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Commentary: severe varicella/zoster and adenovirus infections in immunocompromised patients

W R C Weir

Both chickenpox and shingles have reputations for being relatively mild. One tends to be regarded as a routine childhood infection, the other as a nuisance – sometimes considerable – in old age. Adenoviruses affecting the immunocompetent host likewise have a reasonably benign clinical repertoire. The advent of powerful immunosuppressive therapies and HIV infections, together with an aging population, has altered this benign scenario. Nonetheless, death from infectious disease – even in immunocompromised patients – should always be regarded as preventable.

In the April issue of *Thorax* (pages 422-3) Gatnash and Connolly described the case of a 49 year old asthmatic man, immunocompromised by oral corticosteroids and weekly doses of methotrexate, who acquired chickenpox from his son. The son's rash had appeared three weeks before his father was admitted with chickenpox pneumonia which caused his death. The father's rash had developed five days before his admission and treatment with intravenous acyclovir was

started on the day of admission. Ideally, he should have had serological testing for herpes virus varicella/zoster at the time his son's chickenpox first appeared. A negative result would have prompted a dose of zoster immune globulin (ZIG), an effective means of preventing chickenpox.¹ The more vexed question is whether, once the father's chickenpox had developed, earlier admission would have made any difference. A five day delay before starting antiviral therapy might suggest this but, amongst the immunocompromised, there has been no change in the proportion of patients dying with chickenpox since the introduction of acyclovir.¹ Conversely, previously healthy adults (including pregnant women) appear to benefit from acyclovir when they develop chickenpox pneumonia.² It is therefore important to remind all immunocompromised patients of the potential dangers of chickenpox, particularly if they have not previously had it. A clinical history of chickenpox is not necessarily reliable, and testing of all such patients to identify the seronegative cases at risk might also be wise, albeit expensive.

The patient reported by Morice and Lai in this issue (pages 1221-2) was similar to the one discussed above in that his daughter developed chickenpox five weeks before he presented with chickenpox pneumonia. Nonetheless, it was thought that he had had chickenpox as a child and was presumed to be immune. This therefore underlines the necessity for serological testing of patients at risk, regardless of clinical history. The possibility of second true attacks of chickenpox has been raised by some,³ although these may merely be episodes of disseminated skin involvement in patients with herpes zoster.

Adenovirus infection in immunocompetent hosts is, on the whole, harmless. Nonetheless,