CASE REPORT

Polyarticular juvenile idiopathic arthritis treated with methotrexate complicated by the development of non-Hodgkin’s lymphoma

A G Cleary, H McDowell, J A Sills

A 10 year old boy with juvenile idiopathic arthritis is described. He was treated with methotrexate (MTX) for 2 years 8 months, and presented at routine review with hepatosplenomegaly and suspicious bilateral cervical lymphadenopathy, two months after discontinuing therapy. Magnetic resonance scan revealed significant lymphadenopathy around the upper abdominal aorta and coeliac axis. Lymph node biopsy was consistent with non-Hodgkin’s lymphoma, similar to that reported in several adults with rheumatic diseases taking low dose MTX therapy. He was successfully treated with a standard cytotoxic chemotherapy regime, but unfortunately his polyarthritis has subsequently flared some months after completion of his treatment.

CASE REPORT

Clinical findings

A 10 year old boy with a four year history of juvenile idiopathic arthritis (JIA) presented at routine review with bilateral non-tender but firm and suspicious cervical lymphadenopathy. He had hepatosplenomegaly. He had also intermittently been treated with methotrexate (MTX) 7.5 mg per week, for 2 years 8 months; cumulative dose was 1042.5 mg. The MTX had been given by subcutaneous injection for four months prior to its discontinuation because of nausea associated with oral preparations. MTX had been discontinued two months prior to his presentation with lymphadenopathy as his arthritis had been quiescent for one year. He had also intermittently been treated with prednisolone and various combinations of mycophenolate mofetil and azathioprine as therapeutic immunosuppression post-transplantation, with lymphoproliferative disorder; MTX, methotrexate; PTLD, post-transplant lymphoproliferative disorder; EBV, Epstein–Barr virus; JIA, juvenile idiopathic arthritis; LPD, lymphoproliferative disease; CD21.

Pathological findings

Histopathology of a lymph node biopsy revealed T cell rich B cell lymphoma. Most of the larger cells were positive for CD79A, CD20Y, and CD45RA (B cell markers), but negative for CD10, CD15, CD30, EBV, and T cell markers (including CD3, CD4, CD5, CD8, CD43, CD43RO), and dendritic reticulum cells (CD21).

Treatment

The patient was treated according to a standard treatment protocol (LMB89), which consists of six months of cytotoxic chemotherapy. This comprised vincristine, cyclophosphamide, prednisolone, MTX, doxorubicin, cytarabine, and intrathecal MTX. During this treatment programme his arthritis went into remission. At follow up six months after completion of chemotherapy his lymphoma is in remission, but unfortunately his arthritis has recurred, requiring careful consideration of treatment options.

DISCUSSION

The literature relating to lymphoma occurring in patients with rheumatoid arthritis treated with weekly low dose MTX has recently been reviewed; at least 50 cases have been reported. To the best of our knowledge, four children with JIA treated with MTX have developed Hodgkin's lymphoma. Two of these children had evidence of EBV infection associated with their lymphoproliferative disease. Table 1 summarises the characteristics of the cases.

The incidence of non-Hodgkin’s lymphoma in the age group 5–9 years for the period 1968–95 was 6.5 per million per year. At present approximately 100 children at our institution with JIA are treated with MTX. Several other paediatric rheumatology units were contacted (Great Ormond Street, Birmingham, Nottingham, Leeds, and Newcastle). Any other cases of lymphoproliferative disease (LPD) occurring during treatment with MTX were sought, as it was acknowledged that since case reports were not the favoured format for most journals, other cases may exist. In fact only one other case was noted; this was in a child who also had Blackfan–Diamond syndrome and therefore was at increased risk of haematological malignancy (Professor Woo, personal communication).

Post-transplant lymphoproliferative disorder (PTLD) in an immunocompromised host following paediatric renal transplantation has been reported. Srivastava et al reported PTLD in six of 84 renal transplant recipients in one centre. In all of these patients PTLD was associated with EBV infection (primary in five, reactivation in one). All patients received therapeutic immunosuppression post-transplantation, with prednisolone and various combinations of mycophenolate mofetil.

Abbreviations: Abbreviations: CMV, cytomegalovirus; EBV, Epstein–Barr virus; JIA, juvenile idiopathic arthritis; LPD, lymphoproliferative disease; MTX, methotrexate; PTLD, post-transplant lymphoproliferative disorder
Table 1 Characteristics of patients with juvenile arthritis developing lymphoma while treated with MTX

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Diagnosis</th>
<th>Cell type</th>
<th>Duration of MTX therapy</th>
<th>Other therapy during treatment with MTX</th>
<th>Outcome</th>
<th>Remission of LPD on stopping MTX</th>
<th>Outcome of LPD</th>
<th>Outcome of MTX</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Systemic JIA Mixed cellularity Hodgkin’s lymphoma</td>
<td>CD30 &amp; CD15 EBV pos</td>
<td>16 months</td>
<td>Prednisolone</td>
<td>Late LPD relapse</td>
<td>Partial remission</td>
<td>Yes</td>
<td>12 months</td>
<td>Removal of MTX</td>
</tr>
<tr>
<td>3</td>
<td>Polyarthritis (RF positive) Nodular sclerosing Hodgkin’s lymphoma</td>
<td>CD30 &amp; CD15, EBV pos</td>
<td>33 months*</td>
<td>Not known</td>
<td>Remission of LPD and JIA</td>
<td>Yes</td>
<td>12 months</td>
<td>Partial remission</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Polyarthritis (RF negative) Nodular sclerosing Hodgkin’s lymphoma</td>
<td>CD30 &amp; CD15, CD20, LMP1, EBV pos</td>
<td>30 months†</td>
<td>Prednisolone</td>
<td>EBV positive</td>
<td>Not applicable</td>
<td>Death (respiratory failure secondary to legionella pneumonia)</td>
<td>Remission of LPD and JIA</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Polyarthritis Non-Hodgkin’s lymphoma</td>
<td>CD79A &amp; CD20, CD45RA &amp; EBV neg</td>
<td>32 months</td>
<td>Prednisolone</td>
<td>Intra-articular steroids</td>
<td>Remission of LPD</td>
<td>Relapse of polyarthritis</td>
<td>12 months</td>
<td>Removed after one year due to relapse</td>
</tr>
</tbody>
</table>

*MTX discontinued for eight weeks during proved EBV infection 21 months prior to presentation with nodular sclerosing Hodgkin’s lymphoma.
†MTX discontinued for two months during episode of intercurrent pneumonia.
‡MTX discontinued after 20 months due to disease remission, and recommenced after one year due to relapse.

MTX interferes with the handling of EBV infected lymphocytes, allowing the subsequent proliferation of EBV infected lymphocytes. MTX is an established and effective treatment for polyarthritis in children. It is not clear how physicians caring for children with polyarthritis should interpret these isolated case reports, as there is no epidemiological or proven causal association between therapeutic immunosuppression and the development of LPD. Another dilemma that has been raised by the subsequent clinical course in our patient has been the relapse of his polyarthritis some months after completing chemotherapy for his non-Hodgkin’s lymphoma. His family are understandably very concerned about the potential impact of further immunosuppressant therapy.

Children with polyarthritis are being treated earlier, with larger doses and for longer durations with MTX. Only with data collected prospectively and collaboratively will it be possible to clearly define the risk of LPD in this group. Vigilant clinical observation for the development of lymphoproliferative disorder is recommended as a routine part of the clinical follow up of all children with JIA treated with weekly low dose MTX, especially as routine haematological monitoring is unlikely to alert physicians to the diagnosis.
REFERENCES

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doi: 10.1136/adc.86.1.47

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