Shingles: More than Meets the Eye

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INTRODUCTION

Methotrexate (MTX), a synthetic antifolate, initially came into medical use for cancer treatment in high doses. Due to its high efficacy and low toxicity in low-dose (7.5-25 mg, taken once a week), MTX is the first-line disease-modifying antirheumatic drug (DMARD).1 Side effects and toxicity are associated with dose-dependent mechanisms or, rarely, are due to an idiosyncratic reaction. They are moderate and resolved after drug discontinuation. Nevertheless, although rare, MTX can induce severe, potentially life-threatening adverse effects such as pulmonary toxicity, myelosuppression, and opportunistic infections (Pn jirovecii, disseminated herpes zoster/shingles).2-4 The prevalence of hematologic toxicity, including leucopenia, thrombocytopenia, anemia and pancytopenia, is estimated to be 2-4% of the registered cases.5 Pancytopenia has been reported in around 1.0%-1.4%.5,6 It is a potentially fatal complication associated with significant mortality. We presented a female patient with severe drug reaction including disseminated shingles, oral mucositis and pancytopenia only three days after starting a therapeutic low-dose of MTX.

CASE REPORT

A 65-year-old female patient to the Department of Infectious Disease, University Hospital St. George on March 14, 2016 because of a painful lesion in her mouth, tingling sensation and pain on the left side of her body of 7-day duration. An inching rash appeared the previous day. She also reported a low-grade fever and loose stools. Initially she considered her newly acquired denture as a reason for these complaints and didn’t see a doctor. As her condition worsened she saw a doctor and was referred to this hospital.

On physical examination she was afebrile with normal vital signs. A painful ulcer on her right buccal mucosa and grouped vesicles and pustules in the T10 distribution on the right were noted. There were numerous outlying vesicles on her face...
and abdomen (Figs 1, 2). In addition, a painless skin ulcer on her right sole was seen. The rest of her physical exam was unremarkable. Her medical history was notable only for hypertension, controlled by amlodipine. However, her blood investigations suggested bone marrow suppression and altered renal function (creatinine 171; 140 µmol/l (normal range, 44-96)) (Table 1, Table 2). She was diagnosed with disseminated zoster and was started on acyclovir 3×0.75/24, ceftriaxone 2.0/24, fluconazole 0.2/24 and gabapentin, recommended by a neurologist. The consultant hematologist didn’t recommend further investigation and treatment. However, there was no apparent explanation for the patient’s disseminated zoster, mucositis and pancytopenia. After further inquiry the patient revealed that in late February, while staying with her son in another city, she was prescribed methotrexate 2.5 mg every other day for suspected gout by a rheumatologist. Subsequently this diagnosis was not confirmed but the medication was not cancelled by the doctor. When she got back home she took the first dose MTX on March 2 and the second one 2 days later. On the 3rd day after starting MTX treatment she felt pain in her mouth, which made her eating and drinking very difficult and she withdrew the medication. This new information changed our diagnostic reasoning towards suspected adverse MTX reaction. Repeat consultation with the hematologist confirmed this suspicion and the patient was diagnosed with idiosyncrasy to MTX. She was prescribed folic acid (Leucorin), folic acid and granulocyte-colony stimulating factor (G-CSF). On the same day (day 9 after admission) her repeat blood tests showed spontaneous recovery of white blood cell and thrombocytopenia switched to thrombocytosis (data not shown), which made folic acid and G-CSF administration unnecessary. Her oral mucositis gradually improved as did the rash. She was discharged after 14 days of treatment with recommendation for acetylsal treatment. During the follow-up 14 days and 30 days later her complete blood cell (CBC) returned to normal. One year later she was in good condition and with normal CBC.

**DISCUSSION**

Our case is unique in the sense that disseminated shingles, oral mucositis and pancytopenia developed...
following only 2 doses of low-dose MTX that points towards an idiosyncratic reaction.

MTX in low doses is commonly used as a DMARD and is indicated for rheumatoid arthritis and psoriasis. MTX is structurally similar to folic acid, which is important for cell proliferation. It inhibits the enzyme dihydrofolate reductase, resulting in blocking intracellular DNA synthesis and cell proliferation. Tissues with rapid turnover (oral mucosa, gastrointestinal tract, bone marrow cells) are most susceptible to its cytotoxic effect.7 Efficacy of low dose MTX might be the result of an anti-inflammatory, immunosuppressive and immunotoxic effect.8

However, severe adverse effects can occur, although rarely, even in low-dose therapy. They can be classified into four categories: dose-dependent effect, idiosyncratic effect, effect due to cumulative dose and delayed effect after discontinuation of the drug (teratogenicity).7 The first category includes mucocutaneous and gastrointestinal toxicity and eventually pancytopenia, which can also be due, however, to an idiosyncratic effect (the second group). The side effects of the first and the second group comprise acute MTX toxicity. The cumulative dose adverse effect (the third group) includes chronic hepatitis and pulmonary toxicity. Moreover, some patients might develop pulmonary toxicity with low MTX doses, suggesting an idiosyncrasy.

Pancytopenia usually occurs as a dose-dependent mechanism. Rarely, as in our case, it is an idiosyncratic side effect, usually presenting within the first 10 days of treatment.9,10 The later reaction appears to be an immunological or hypersensitivity-

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Table 1. Initial laboratory investigations of the patient

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Measured Day 1</th>
<th>Measured Day 3</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/l)</td>
<td>96</td>
<td>93</td>
<td>120-160</td>
</tr>
<tr>
<td>Red cell count (×10^12/l)</td>
<td>3.36</td>
<td>3.31</td>
<td>3.9-5.3</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>84.5</td>
<td>87.1</td>
<td>82-98</td>
</tr>
<tr>
<td>White cell count (×10^9/l)</td>
<td>2.58</td>
<td>2.63</td>
<td>3.5-10.5</td>
</tr>
<tr>
<td>Neutrophils (×10^9/l)</td>
<td>31.5</td>
<td>42.3</td>
<td>42%-70%</td>
</tr>
<tr>
<td>Lymphocytes (×10^9/l)</td>
<td>52.7</td>
<td>30.5</td>
<td>22%-48%</td>
</tr>
<tr>
<td>Platelets (×10^9/l)</td>
<td>32</td>
<td>89</td>
<td>140-400</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>32</td>
<td>90</td>
<td>2-30</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>95</td>
<td>0-10</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Laboratory evaluation & diagnostic procedures

<table>
<thead>
<tr>
<th>Biochemistry</th>
<th>Measured Day 3</th>
<th>Measured Day 8</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>K (mmol/l)</td>
<td>4.1</td>
<td>3.9</td>
<td>3.5-5.6</td>
</tr>
<tr>
<td>Na (mmol/l)</td>
<td>138</td>
<td>140</td>
<td>136-151</td>
</tr>
<tr>
<td>urea (mmol/l)</td>
<td>84.5</td>
<td>87.1</td>
<td>2.6-7.2</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>171.0</td>
<td>140.0</td>
<td>44-96</td>
</tr>
<tr>
<td>Protein (g/l)</td>
<td>57</td>
<td></td>
<td>60-83</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>33</td>
<td></td>
<td>35-52</td>
</tr>
<tr>
<td>ALAT (U/l)</td>
<td>16</td>
<td>24</td>
<td>140-400</td>
</tr>
<tr>
<td>ASAT (U/l)</td>
<td>29</td>
<td>42</td>
<td>2-30</td>
</tr>
<tr>
<td>Ur Ac (µmol/l)</td>
<td>214</td>
<td>95</td>
<td>149-363</td>
</tr>
</tbody>
</table>
ity phenomenon, which is unpredictable. Genetic polymorphism has been implicated as a predictive factor for MTX toxicity.11,12 Pancytopenia usually has been preceded by mucositis, as the accumulation of MTX is higher in mucosal epithelial cells than in bone marrow stem cells.13 It is considered a warning sign. Low-dose MTX appears to be associated with minimal, if any, risk of infection. Nevertheless, patients with neutropenia and mucositis as a result of MTX myelosuppression are at relative risk of infection. Patel et al.14 similar to our patient, reported a patient with disseminated zoster and rheumatoid arthritis on low-dose MTX for 8 years. We believe that it was the pancytopenia that triggered the disseminated shingles in our case.

MTX toxicity is related to folate antagonism and/or folate deficiency. Predisposing factors include advanced age, impaired renal function, hypoalbuminemia, concurrent use of drugs known to interact with MTX (trimethoprim/sulfamethoxasole, penicillin G and nonsteroidal anti-inflammatory drugs). It may also occur as an incidental overdose (daily instead of weekly). The most important factor is the impaired renal function.15 MTX is eliminated unchanged through the kidneys and even a mild renal dysfunction can predispose to severe pancytopenia.5 These risk factors were not identified in our patient. However, as creatinine clearance had not been calculated impaired renal function could not have been ruled out.

Management of MTX myelosuppression includes withdrawal of MTX, administration of folinic acid as an antidote of MTX, G-CSF in severe cases, aggressive fluid and broad spectrum antibiotics. The bone marrow function is gradually restored within 2 weeks.16 Mortality depends on the time taken for the recovery and the severity of pancytopenia.17 According to Kuitunen et al.,18 morbidity was 100% if correction of leucopenia was not achieved until day 5. Fortunately, our case experienced spontaneous recovery. Although pancytopenia was rarely observed, in 24%-44% of the cases with fatal outcome the most important cause of death was infection.17,19

To prevent toxicity the patients should be carefully selected and provided with written instruction on prescription regimen to prevent administration errors. A proper monitoring of CBC count and biochemistry during MTX treatment is essential to reduce the potential serious toxicity.20 Nevertheless, due to the rapid onset of myelosuppression, its early detection is a challenging task even if monthly blood monitoring is regularly performed during the follow-up.9,20

CONCLUSION

Our case presented with shingles, mucositis and pancytopenia initially not consistent with the underlying disease. However, there was more to the skin rash than meets the eye. The patient’s initial history taking had missed MTX intake 10 days before and the patient reported only current medications. Arriving at the correct diagnosis in difficult cases, as in the case presented, requires further evaluation, including repeat history taking and eliciting more details if diagnosis remains elusive.

REFERENCES


Опоясывающий лишай: больше, чем кажется на первый взгляд

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Небольшая доза метотрексата (МТ) является модифицирующим заболевание антиревматическим агентом первой линии (МЗАРА) для лечения ревматоидного артрита и псориаза. Хотя считается, что метотрексат имеет профиль безопасности, он часто может вызывать серьёзные побочные эффекты, такие как панцитопения, мукозит, заболевание почек и печени. Оральный мукозит должен служить сигналом для врачей о токсичности МТ. Мы сообщаем о 64-летней женщине с тяжёлой лекарственной реакцией, включающей опоясывающий лишай, оральный мукозит и панцитопению, всего лишь через три дня после начала приёма терапевтической дозы МТ. Первоначально мукозит и миелосупрессия не могли быть связаны с основным заболеванием. При уточнении анамнеза пациента был пропущен факт приёма МТ за 10 дней до этого, а больной сообщил только о текущем приёме лекарств. Независимо от этого, кожно-мышечная сыпь скрывала нечто большее, чем могло показаться на первый взгляд. Только после дополнительного разговора с пациентом нам о приёме двух доз МТ и о последующем прекращении приёма препарата. Постановка правильного диагноза при трудных случаях, как это случилось в описанном случае, требует тщательной оценки, включая как повторное уточнение анамнеза, так и установление дополнительных деталей при невозможности поставить диагноз.