The first Aotearoa New Zealand case of NUDT15-variant-related thiopurine-induced myelotoxicity

Ho Nam Lee, Steven Leslie Ding

ABSTRACT

A 37-year-old Han Chinese man, with a history of severe ulcerative colitis with incomplete response to oral glucocorticoids, was commenced on azathioprine [AZA] 200mg once a day. His pre-treatment thiopurine S-methyltransferase [TPMT] levels were in the normal range. Eleven days later he developed symptoms of stomatitis and gingivitis. Chinese herbal medications were taken in an attempt to treat these symptoms. He presented to the emergency department with this, with normal vital signs. A full blood count five days post-onset of symptoms showed pancytopenia with an absolute neutrophil count [ANC] of 0.0x10^9/L, C-reactive protein was 120 mg/L. Initial chest radiograph, urinalysis and peripheral blood cultures were unremarkable and he was commenced on broad spectrum antibiotics and granulocyte colony stimulating factor [G-CSF]. He remained an inpatient under the gastroenterology team for 16 days and developed infectious complications of herpes simplex stomatitis, oral candidiasis, dental abscess, and scalp abscess. On day 16 his ANC recovered to 1.0x10^9/L and was discharged from the hospital. He underwent nudix hydrolase 15 [NUDT15] genotyping and was found to have homozygosity for the variant NUDT15:c.415C>T. This case demonstrates the importance of pre-treatment testing for NUDT15 genetic variants, to predict the risk of severe leucopaenia, particularly in a patient of East Asian ethnicity.

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hiopurines, such as azathioprine, 6-mercaptopurine, 6-thioguanine, are used commonly as steroid sparing agents and immuno-suppressants for many auto-inflammatory conditions such as inflammatory bowel disease [IBD], anti-neutrophil cytoplasmic antibody [ANCA] associated vasculitides, rheumatic conditions, and solid organ transplantation.

Their side effects include gastrointestinal symptoms, acute pancreatitis, myelosuppression, and neoplasms. Patients are routinely screened for TPMT genetic polymorphisms prior to commencing therapy with azathioprine to predict the risk of severe myelosuppression and azathioprine intolerance. Recently, genetic testing for polymorphisms in the enzyme NUDT15 has attracted interest as another predictor of severe myelosuppression, especially in East Asian patients.

We describe the first case of severe myelotoxicity related to a NUDT15 genetic variant in Aotearoa New Zealand.

Case presentation

A 37-year-old Han Chinese gentleman with a recent diagnosis of severe ulcerative colitis with incomplete response to oral steroids was started on AZA 200mg once a day following normal TPMT serum levels as part of pre-treatment screening. Eleven days later he developed stomatitis with pain on chewing and swallowing. He also noticed alopecia, right post-auricular swelling, pain and serous discharge from the vertex of the scalp. He had ongoing diarrhoea, albeit improved with oral prednisone. He had no respiratory, genito-urinary, musculoskeletal, cutaneous, or B-symptoms. Chinese herbal medicines were commenced at this time by the patient for these symptoms. On day 16 post-commencement of AZA he obtained a blood test which revealed a new pancytopena with an ANC of 0.0x10^9/L. He was contacted that night and in the absence of concerning symptoms, was advised to present to the emergency department at Christchurch Hospital the following day, to be seen by the gastroenterology team for assessment and treatment. His vital signs were all within normal range and clinical examination revealed gingivitis and mucositis of the oral mucosal surface. There was no oral thrush. The right post-auricular area was indurated and tender to touch with no fluctuance or discharge.

Investigations

Upon admission the full blood count showed an ANC of 0.01x10^9/L, with a total white blood cell count of 0.9x10^9/L, a platelet count of 55x10^9/L and a haemoglobin level of 108g/L. The mean cell volume was normal at 94fL. His mouth swab revealed presence of herpes simplex virus as well as growth of Candida albicans. Non-contrast computed tomography scan of the head did not reveal any evidence of mastoiditis or extra-axial collection. His chest radiograph did not show any evidence of a pneumatic...
process. An orthopantomogram revealed periapical lucency about the mesial root of tooth 46 that could have represented an abscess. Faecal samples had no evidence of viral or bacterial infection. The urinalysis had no pyuria with white cells less than 10x10⁶/L and there was no growth on culture. Numerous pre-antibiotic peripheral blood cultures exhibited no growth. He was also negative for hepatitis A, B, C, and human immunodeficiency virus. Cytomegalovirus DNA in the plasma was also undetectable.

NUDT15 genotyping revealed that the patient was homozygous for the variant NUDT15:c.415C>T.

Progress and treatment

Broad spectrum intravenous antibiotics were commenced following peripheral blood culture collection upon admission. AZA was ceased at admission while daily subcutaneous G-CSF 300mcg, oral fluconazole 50mg and 8-hourly intravenous acyclovir 800mg initiated. Dental extraction of infected tooth 46 under local anaesthetic by the dental team was completed, which was uneventful.

Due to ongoing pain in the temporo-occipital region of the scalp an ultrasound scan was performed which showed a small, complex soft tissue fluid collection measuring 23mm in length and 4mm in depth. Ultrasound-guided aspirate of this scalp collection was performed with a gram stain showing numerous leucocytes with no organisms and no growth in culture.

A sample of the herbal medicines was taken for toxin analysis and was negative for heavy metals or active drugs. There was no evidence for interaction between these and AZA, nor alteration of TPMT activity or direct myelotoxicity.

He remained an inpatient for 17 days total, with daily monitoring of full blood counts and inflammatory markers (please see Table 1). G-CSF was continued until ANC was above 1.0x10⁹/L for two days. After cessation a reduction in ANC was observed the following day, however, this improved in the following days despite continued cessation of G-CSF.

He completed the full course of antibiotics and anti-fungals while an inpatient and was discharged from hospital with an ANC of 1.0x10⁹/L and a short course of oral acyclovir. Full blood count monitoring continued in the community which showed improving pancytopenia (Table 2). Follow up in clinic three months following discharge from hospital confirmed that the patient was clinically well.

Discussion

DNA variants in the TPMT gene have been described which can lead to a reduction in TPMT enzymatic activity and metabolism of thiopurines and their metabolites. As a result, life-threatening myelotoxicity can complicate thiopurine therapy. Ninety percent of Caucasians have high or normal TPMT activity, whereas 10% have intermediate activity and 0.3% have low or no detectable enzyme activity. Inter-ethnic variations have been described with 5% of East Asians having intermediate enzyme activity and 0.12% having low or undetectable activity.

Although the frequency of TPMT mutations is lower in East Asian populations the frequency of thiopurine-induced leucopaenia can be higher. Genome wide association studies [GWAS] in IBD adult patients in Korea, and acute lymphocytic leukaemia paediatric patients in North America, has led to the discovery of genetic variations of the NUDT15 enzyme in patients with thiopurine-induced leucopaenia. Subsequent retrospective studies in China and Japan have investigated NUDT15 genetic polymorphisms and its role in thiopurine-induced leucopaenia in IBD patients.

In contrast to TPMT mutations, NUDT15 mutations are found more commonly in East Asian patients than that of Caucasians. The incidence of NUDT15 allelic mutations in East Asian populations is between 8.5–16%. In Caucasians it is less than 1%. To date, there are no data in the literature regarding NUDT15 polymorphisms in the Māori and Pacific Island populations.

The Clinical Pharmacogenetics Implementation Consortium have released guidelines for thiopurine dosing based on NUDT15 genotypes. For a NUDT15 intermediate metaboliser patient, AZA should be commenced at a starting dose of 30–80% of normal dose with regular monitoring. However, in a NUDT15 poor metaboliser, it is recommended that an alternative non-thiopurine immuno-suppressant should be considered for non-malignant conditions (such as IBD), while for malignant conditions a starting dose of 10% of normal dose is recommended.

Conclusion

This is the first case, in Aotearoa New Zealand, of severe thiopurine-induced leucopaenia associated with a patient who was found to be a NUDT15 poor metaboliser. We recommend pre-treatment genotype testing of TPMT in all patients. In addition, all East Asian patients are recommended to have NUDT15 genotype testing prior to initiation of a thiopurine to estimate the risk of myelosuppression. In the Caucasian population NUDT15 testing should be considered in patients who develop myelosuppression. Currently there is limited data in relation to the genotype and phenotype of NUDT15 polymorphisms in the Māori and Pacific Island populations and further studies in these ethnic groups would be beneficial.
**Table 1:** Full blood count monitoring during inpatient admission.

<table>
<thead>
<tr>
<th></th>
<th>D-1</th>
<th>D0</th>
<th>D1</th>
<th>D3</th>
<th>D5</th>
<th>D7</th>
<th>D9</th>
<th>D11</th>
<th>D13 (G-CSF ceased)</th>
<th>D15</th>
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<tbody>
<tr>
<td>Haemoglobin (g/L)</td>
<td>109</td>
<td>108</td>
<td>96</td>
<td>97</td>
<td>88</td>
<td>93</td>
<td>81</td>
<td>76</td>
<td>95</td>
<td>97</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>76</td>
<td>55</td>
<td>30</td>
<td>22</td>
<td>42</td>
<td>59</td>
<td>67</td>
<td>64</td>
<td>77</td>
<td>69</td>
</tr>
<tr>
<td>White blood cells (x10^9/L)</td>
<td>0.4</td>
<td>0.9</td>
<td>0.02</td>
<td>1.0</td>
<td>1.0</td>
<td>1.3</td>
<td>1.4</td>
<td>1.6</td>
<td>2.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Neutrophils (x10^9/L)</td>
<td>0.0</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
<td>0.06</td>
<td>0.22</td>
<td>0.38</td>
<td>0.7</td>
<td>1.1</td>
<td>0.9</td>
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**Table 2:** Full blood count monitoring post discharge.

<table>
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<tr>
<th></th>
<th>Day 2 post discharge</th>
<th>Day 10 post discharge</th>
<th>One month post discharge</th>
<th>Two months post discharge</th>
<th>Three months post discharge</th>
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<tr>
<td>Haemoglobin (g/L)</td>
<td>88</td>
<td>89</td>
<td>100</td>
<td>121</td>
<td>126</td>
</tr>
<tr>
<td>Platelets (x10^9/L)</td>
<td>91</td>
<td>188</td>
<td>247</td>
<td>133</td>
<td>102</td>
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<tr>
<td>White blood cells (x10^9/L)</td>
<td>2.4</td>
<td>3.8</td>
<td>3.9</td>
<td>3.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Neutrophils (x10^9/L)</td>
<td>1.4</td>
<td>2.6</td>
<td>1.4</td>
<td>1.1</td>
<td>1.3</td>
</tr>
</tbody>
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COMPETING INTERESTS
Nil.

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REFERENCES