CASE REPORT

Resolution of ipilimumab induced severe hepatotoxicity with triple immunosuppressants therapy

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SUMMARY

We describe a case of a patient from Far North Queensland, Australia, with life-threatening hepatotoxicity caused by ipilimumab induced immune-related adverse events (irAEs). Our patient presented with non-specific symptoms including malaise, lethargy and fevers. Her work up revealed acute hepatitis, which was presumed to be related to ipilimumab treatment for her metastatic melanoma. Causality for ipilimumab was assessed with the CIOMS scale (Council for International Organizations of Medical Sciences) and provided a causality level of 'highly probable' (score +9). She was started on methylprednisolone as per guidelines for ipilimumab induced irAEs. On the second day of treatment her transaminases enzymes unexpectedly rose several hundred times. Investigations for other causes of acute hepatitis including abdominal imaging were negative. She was started up front on equine antithymocyte globulin, mycophenolate moefetil and continued on methylprednisolone. She recovered clinically and biochemically in 2 weeks and continues to remain well.

BACKGROUND

Metastatic melanoma is traditionally associated with poor prognosis, with a median survival reported as 9 months with 1 year survival rate of 33%.[1] Queensland has one of the highest incidences of melanoma in the world. Melanoma is sometimes labelled as Australia's national cancer. In 2009, melanoma of the skin was the fourth most commonly diagnosed cancer in Australia (after prostate, bowel and breast cancer), accounting for 10.1% of all new cancers. About 12 500 new cases of melanoma are diagnosed every year in Australia, predominantly in Queensland, accounting for 3.4% of all cancer deaths in Australia.[2] Recently, new therapeutic options for metastatic melanoma have changed its outlook, in particular with immunotherapy. The programmed death 1 (PD-1) inhibitor nivolumab has shown promise when used concurrently with ipilimumab, causing more rapid and deeper clinical tumour response.[3]

Ipilimumab (tradename: Yervoy) is a full human monoclonal antibody directed against cytotoxic T-lymphocyte antigen-4 (CTLA-4), a prominent negative regulator in T-cell activation. Ipilimumab was approved by the Food and Drug Administration (FDA) in March of 2011 for unresectable stage III or IV melanoma. Although ipilimumab has a manageable safety profile, treatment has been associated with potentially fatal adverse effects, most notable immune-related adverse events (irAEs). Most of the serious complications of ipilimumab treatment reported are associated with the gastrointestinal (GI) tract; these include diarrhoea, hepatotoxicity, abdominal pain and bloating. Recently, there have been reports of ipilimumab induced myasthenia gravis complicating treatment of metastatic melanoma.[4] Immune-mediated hepatitis has been reported in 2–9% of patients treated with ipilimumab.[5] At least one death due to liver failure has been reported, which was attributed to a delay in the initiation of treatment.[6]

CASE PRESENTATION

A 50-year-old Caucasian woman from Far North Queensland, Australia, presented with febrile illness associated with rigours and grossly deranged liver function tests with a history of ipilimumab treatment for metastatic melanoma. She was healthy before diagnosis of melanoma and did not take any regular medications. She lived with her husband and did not drink alcohol.

She presented to the emergency department late in the afternoon of Monday 18 November 2013 (day 1) with hypotension, fevers and malaise. Her biochemistry showed grossly altered liver enzymes with an aspartate aminotransaminase (AST) of 936 units/L and alanine aminotransaminase (ALT) of 640 units/L with equally elevated lactate dehydrogenase, alkaline phosphatase and γ-glutamyl transferase . Her bilirubin, however, was normal and blood counts were also largely normal except for minor abnormalities. She did not drink alcohol and denied taking any hepatotoxic medications or herbal treatments in the recent past. Her initial diagnosis was ipilimumab induced irAEs causing hepatitis or drug-induced liver injury (DILI). She was started on 2 mg/kg of methylprednisolone to treat grade III hepatotoxicity according to ipilimumab immune toxicity guidelines. The next morning (day 2), however, her liver enzymes showed an exponential rise to AST of 7280 and ALT of 4700, and minor elevation of bilirubin. There was a concern of fulminant hepatic failure, however, she remained clinically stable without any hepatic encephalopathy. She, however, developed mild coagulopathy the next day. She was seen by gastroenterologists and alternative aetiologies were considered. According to Council for International Organizations of Medical Sciences scale (CIOMS)[7] for hepatocellular injury, the final score calculated was 9. This indicated that the DILI was most probably secondary to ipilimumab, as depicted in table 1.

INVESTIGATIONS

The patient's work up for viral hepatitis including hepatitis A, B, C, E, rickettsia and cryptococcal

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Table 1 Council for International Organizations of Medical Sciences scale (CIOMS) for hepatocellular type of injury[7]

Items of hepatocellular injury	Score	Result
1. Time to onset from the beginning of the drug/herb		
5–90 days (rechallenge: 1–15 days)	2	2
<5 or >90 days (rechallenge: >15 days	1	
2. Course of ALT after cessation of the drug/herb		
Decrease ≥50% within 8 days	3	3
Decrease ≥50% within 30 days	2	
No information or continued drug/herb use	0	
Decrease ≥50% after the 30th day	0	
Decrease <50% after the 30th day or recurrent increase	−2	
3. Risk factors		
Alcohol use (drinks/day: >2 for women, >3 for men	1	0
Alcohol use (drinks/day: ≤2 for women, ≤3 for men)	0	
Age ≥55 years	1	
Age <55 years	0	
4. Concomitant drug(s) or herbs(s)		
None or no information	0	0
Concomitant drug or herb with incompatible time to onset	0	
Concomitant drug or herb with compatible or suggestive time to onset	−1	
Concomitant drug or herb known to be a hepatotoxin and with compatible or suggestive time to onset	−2	
Concomitant drug or herb with evidence for its role in this case (positive rechallenge or validated test)	−3	
5. Search for non-drug/herb causes		
Group I (6 causes) (tick if negative)	–	2
Anti-HAV-IgM	–	
HBsAg, anti-HBc-IgM, HBV-DNA	–	
Anti-HCV, HCV-RNA	–	
Hepatobiliary sonography/colour Doppler sonography of liver vessels/endosonography/CT/MRC	–	
Alcoholism (AST/ALT ≥2)	–	
Acute recent hypotension history (particularly if underlying heart disease)	–	
Group II (6 causes)	–	2
Complications of underlying disease(s) such as sepsis, autoimmune hepatitis, chronic hepatitis B or C, primary biliary cirrhosis or sclerosing cholangitis, genetic liver diseases	–	
Infection suggested by PCR and titre change for CMV (anti-CMV-IgM, anti-CMV-IgG)	–	
EBV (anti-EBV-IgM, anti-EBV-IgG)	–	
HEV (anti-HEV-IgM, anti-HEV-IgG)	–	
HSV (anti-HSV-IgM, anti-HSV-IgG)	–	
VZV (anti-VZV-IgM, anti-VZV-IgG)	–	
All causes groups I and II—reasonably ruled out	2	0
The 6 causes of group I ruled out	1	
5 or 4 causes of group I ruled out	0	
Less than 4 causes of group I ruled out	−2	
Non-drug or herb cause highly probable	−3	
6. Previous information on hepatotoxicity of the drug/herb		
Reaction labelled in the product characteristics	2	
Reaction published but unlabelled	1	
Reaction unknown	0	
7. Response to unintentional readministration		
Doubling of ALT with the drug/herb alone, provided ALT below 5N before re-exposure	3	
Doubling of ALT with the drug(s) and herb(s) already given at the time of first reaction	1	
Increase of ALT but less than N in the same conditions as for the first administration	−2	
Other situations	0	
Total score		9

Total score and resulting causality grading: ≤0: excluded; 1–2: unlikely; 3–5: possible; 6–8: probable; ≥9: highly probable.
ALT, alanine aminotransferase; AST, Aspartate aminotransferase; CIOMS, Council for International Organizations of Medical Sciences; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBc, hepatitis B core; HBsAg, hepatitis B antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; MRC, MR cholangiography; N, Upper limit of the normal range; VZV, varicella zoster virus.

antigen, and extended autoimmune work up, which included antimitochondrial antismooth muscle, antiliver-kidney microsomal, antinuclear and antineutrophil cytoplasmic antibodies, were negative. She underwent ultrasound of the liver, which was unremarkable. Her serum paracetamol level was unremarkable. Her blood cultures performed in the emergency department were negative for growth. Her serology for dengue and leptospirosis was negative. Her serum paracetamol levels were

undetectable. She was positive for cytomegalovirus (CMV) and Epstein-Barr virus IgG. Liver biopsy was not considered safe in such an acutely unwell patient.

DIFFERENTIAL DIAGNOSIS

Our main differential diagnosis was ipilimumab induced irAEs causing hepatotoxicity.

TREATMENT

Our patient initially presented with non-specific symptoms with transaminases up to 30 times the normal limit, which subsequently rose to 230 times the limit in a span of merely hours. This degree of hepatic enzyme elevation with ipilimumab, to the best of our knowledge, has not been reported before. Given the patient's deteriorating clinical course in such a rapid span of time, she was started on methylprednisolone, equine antithymocyte globulin (ATG) (ATGAM) and mycophenolate mofetil up front. She was considered for a liver biopsy before starting of treatment; however, it was deferred because of mild coagulopathy and the emergent life-threatening situation. She received her first dose of methylprednisolone in the emergency department. The next morning, her blood tests showed acute worsening. She was started on ATGAM with mycophenolate mofetil early in the morning of day 2. She tolerated the infusion generally well. This treatment was complicated overnight by asymptomatic sinus bradycardia. Her liver functions showed steep decline after the first dose of ATGAM, which further improved after the second dose on day 3. She was continued on methylprednisolone for a total of four doses, 120 mg each, over days 1–4.

The patient's liver functions improved within 24 h, with a drop in absolute lymphocyte count to 0.07×10^9/L. Her liver functions touched baseline in 2-weeks of treatment. After the four doses of methylprednisolone, she was switched to prednisolone, which she was weaned off in 6 weeks. Mycophenolate was continued at 1 gm two times per day and subsequently halved, and finally stopped in 2 weeks. Table 2 below shows the level of liver enzymes, absolute lymphocyte counts and effect of treatment with triple immunosuppressant treatment on both parameters from day 0 to day 30.

Our patient was administered ATGAM with good response. We were able to keep absolute lymphocyte counts to $<0.1\times10^9$ by administering ATG, without any side effects. The patient's absolute lymphocyte count remained below 0.1 for at least 3 days during her treatment. She was started on prophylaxis with trimethoprim/sulfamethoxazole and valacyclovir, for pneumocystis jirovecii and CMV, respectively. In renal transplantations, rabbit ATG (thymoglobulin) is the standard of care; it has proved to be superior in acute renal allograft rejection settings. Compared with ATGAM, rabbit ATG (thymoglobulin) resulted in a higher rate of reversal of rejection (88% vs 76%) and a lower rate of recurrent rejection at 90 days after antibody therapy (17% vs 36%). Patient and graft survival and the rates of adverse events and infections were similar in both groups.[8] We chose ATGAM for our patient as thymoglobulin was not available in our centre at the time.

OUTCOME AND FOLLOW-UP

The patient continues to be well with regard to liver functions; unfortunately, however, 4 months after the last dose of ipilimumab, she developed progressive disease, which involved development of new lesions in the pancreas and enlargement of her previous metastatic deposits. On further investigation, she was found to carry N-RAS mutation in a previous sample. She is currently being considered for participation in a clinical trial with MEK (mitogen-activated protein kinase) inhibitor for her N-RAS mutated metastatic melanoma. The N-RAS clinical trial is randomising patients between a MEK inhibitor versus chemotherapy with dacarbazine.

DISCUSSION

There is one case report in the literature, where triple immunosuppressants were used sequentially in patients with irAE-related hepatotoxicity following relapse after initial response to steroids.[9] To the best of our knowledge, our patient was the first to be treated with ATGAM for this condition along with mycophenolate mofetil and methylprednisolone. Also, it was used up front for the first time, for unprecedented severe life-threatening hepatotoxicity caused by immune-related mechanisms. Our patient recovered completely after receiving two doses of ATGAM in combination with mycophenolate mofetil and methylprednisolone over a longer period of time. This case report indicates that robust immunosuppressant therapy can potentially prevent fatality caused by irAEs. These adverse events may include skin toxicity, including rashes, which may rarely progress to life-threatening toxic epidermal necrolysis. They can involve the GI tract, causing colitis, characterised by mild to moderate, but occasionally also severe and persistent, diarrhoea. They can also cause hypophysitis, hepatitis, pancreatitis, iridocyclitis, lymphadenopathy, neuropathies and nephritis. Early recognition of irAEs and initiation of treatment are critical to reduce the risk of sequelae. Interestingly, irAEs correlate with treatment response in some studies.[10] Several large studies have reported increased efficacy in patients affected by irAEs with responses in 26% of patients experiencing any irAE compared with 2% in patients who did not experience any irAE. There was also a 'severity-response-effect' with response rates of 22% and 28%, in patients with grades 1/2 and 3/4 adverse reactions, respectively.[11]

Table 2 Liver function tests and absolute lymphocyte count during treatment

Test	Normal range	D0 Baseline	D1 MEP 1st dose	D2 MEP 2nd and ATGAM 1st dose	D3 MEP 3rd and ATG 2nd dose	D4 MEP 4th	D15	D30
ALT	<34 U/L	19	640	4700	1460	1520	40	20
AST	<31 U/L	16	936	7280	265	205	35	18
GGT	<38 U/L	29	186	244	174	181	30	25
ALP	42–98 U/L	91	366	604	326	304	89	76
Bilirubin (total)	<20 μmol/L	11	15	30	12	12	11	9
Absolute lymphocyte count	$1–4\times10^9$	1.47	1.08	0.86	0.07	0.08	1.1	2.2

ALP, alkaline phosphatase; (ATGAM) Horse anti thymocytic globulin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT,γ-glutamyl transferase; MEP, methylprednisolone.

Hepatotoxicity is reported in only 3–9% of patients on ipilimumab, and usually manifests as an asymptomatic increase of transaminases and bilirubin. It is prudent to rule out possible causes (eg, infectious, metabolic and from alcohol abuse) in patients with hepatotoxicity. In our patient, we ruled out all possible causes of acute hepatitis. Patients may develop elevated ALT, AST and/or hyperbilirubinaemia in the absence of clinical symptoms. Importantly, biopsies from patients experiencing immune-related hepatotoxicity showed diffuse T-cell infiltrates consistent with immune-related hepatitis.[12] In a phase II study, 84% patients experienced drug-related irAEs with 43 patients (28%) had grade 3–4 events. One of the fatalities was a treatment-related death by liver failure and occurred in a patient receiving ipilimumab 10 mg/kg who was not treated with systemic corticosteroids promptly.[13]

Also, our case highlights that at least some of the autoimmune side effects can be refractory to first-line or second-line immunosuppression and therefore effective third-line immunosuppressive therapies are required. Also, in some of these cases, rapid immunosuppression due to acuity of the situation is required; there is a need to develop such protocols. Our patient was essentially treated on the lines of acute allograft rejection. Also, in a recently published phase 1 study, an anti-PD-1 antibody (BMS-936558) showed responses in non-small cell lung cancers, melanoma and renal cell cancers.[14] In this study, the incidence of grade 3/4 hepatotoxicity was reported to be 1% or less. These drugs are thought to be less immunotoxic given that they are more specific immunostimulants. Given the potential usage of immunotherapy across multiple common tumour types, these immune-related side effects are going to be seen in greater numbers. Recently, the anti-PD-1 antibody lambrolizumab was found to be effective in patients who progress on ipilimumab.[15]

Interestingly, Oncology, more than any other specialty, has recently been exposed to an array of new drugs. In 2013, The US FDA approved 139 new drugs of which half are for the treatment of cancers and orphan diseases.[16] Given the unprecedented progress in the field of medical oncology, it is prudent for all healthcare workers to be vigilant for the detection of expected or unexpected side effects of these novel treatments and to consider their management, to prevent fatality. International guidelines addressing management of these side effects should be formulated and made available to clinicians using these medications.

Patient's perspective

"To be advised I may have 48 hours to live is a very scary moment. The procedures taken place allowed me to survive and I am very lucky to be able to write this and to thank everyone involved that were in a position to make critical decisions. Makes me very proud to be treated by amazing professionals. Myself and my family are blessed to have this care"
Written by patient involved on 05/11/2014

Learning points

- There should be a high index of suspicion for immune related adverse events (irAEs), especially hepatotoxicity, which should be treated with proper immunosuppressive treatment to prevent fatality in any patient on immunotherapy. Given the current widespread use of ipilimumab for metastatic melanoma, irAEs should be considered if a patient presents with sudden unexplained clinical deterioration, as these can involve any organ system.
- As potential usage of immunotherapy increases across multiple common tumour types, irAEs will be seen in greater numbers.
- Given the unprecedented progress in the field of medical oncology, it is prudent for all healthcare workers to be vigilant for detection of expected or unexpected side effects of these novel treatments and to consider their management, to prevent fatality.
- International guidelines addressing management of these side effects should be formulated and made available to clinicians using these medications.

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