

PEG-asparaginase induced severe hypertriglyceridemia

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SUMMARY

Asparaginase (ASP) is an effective chemotherapy agent extensively used in children with acute lymphocytic leukemia (ALL). There has been a recent interest in using ASP in adults with ALL, particularly the less toxic pegylated (PEG) formulation. Hypertriglyceridemia (HTG) is a rare complication of PEG-ASP therapy. We report two cases of obese patients who developed severe HTG after receiving PEG for ALL. Both patients were incidentally found to have severe HTG (TG of 4,330 and 4,420 mg/dL). In both patients, there was no personal or family history of dyslipidemia or hypothyroidism. There was no evidence of pancreatitis or skin manifestations of HTG. Both patients were treated with PEG cessation, low-fat diet and pharmacotherapy. Both patients were re-challenged with PEG, with subsequent increase in TG but no associated complications. TG returned to baseline after discontinuing PEG and while on therapy for HTG. A literature review of PEG-induced HTG in adults demonstrated similar results: asymptomatic presentation despite very severe HTG. HTG is a rare but clinically important adverse effect of PEG. Underlying obesity and/or diabetes may represent risk factors. Clinicians should monitor TG levels during PEG therapy to avoid TG-induced pancreatitis. *Arch Endocrinol Metab.* 2016;60(2):173-7

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INTRODUCTION

L-Asparaginase (ASP) has been a key component of the chemotherapy regimens used for acute lymphocytic leukemia (ALL) in children for 50 years (1). ASP combined with polyethylene glycol (PEG-ASP) is a long-acting formulation with a half-life of 6 days that allows for intramuscular or intravenous administration (1). There has been a recent interest in using ASP in adults with ALL, particularly the less toxic pegylated formulation: PEG-ASP. The literature on ASP toxicities is mainly from the pediatric population, with just few reported cases in adults. ASP-related toxicity includes: pancreatitis, liver toxicity, thrombosis, hyperglycemia, hypersensitivity reactions, hyperviscosity syndrome, osteonecrosis and lipemia retinalis (1-3). Asymptomatic hypertriglyceridemia (HTG) has also been reported (4,5) but with just few case reports in adults (6-13). Here, we describe two adults with asymptomatic PEG-associated severe HTG and provide the first literature review of adults with PEG-induced HTG.

MATERIALS AND METHODS

Retrospective data from the electronic medical records at North Shore-LIJ Health System was collected. Both patients were receiving care at our cancer center and presented within few weeks of each other. A PubMed search of the following terms: “Asparaginase” [Mesh] AND “Hypertriglyceridemia” [Mesh] AND “Adult” [Mesh] was performed. Relevant studies from retrieved references were also reviewed. We present the first review of adult cases of PEG-induced HTG.

RESULTS

Patients

Patient 1 is a 44 year-old morbidly obese (BMI 54 kg/m²) female receiving chemotherapy for ALL, including PEG. The patient has a past medical history of hyperthyroidism (now euthyroid) and controlled type 2 diabetes. She received 5 doses of PEG (5750 IU) over a period

of 6 months. During a scheduled follow-up appointment, after her 5th dose of PEG, the laboratory reported the serum to be lipemic. The lipid panel revealed severe HTG: triglycerides (TG) 1320 mg/dL (Figure 1). Three weeks later, her TG level declined to 306 mg/dL. She then received an additional dose of PEG. As part of the chemotherapy regimen, she also received hydrocortisone 100 mg IV, intrathecal cytosine arabinoside, vincristine and daunorubicin. Few days after, a follow up test revealed TG level of 4,330 mg/dL. At that time she was hospitalized for HTG. She did not complain of abdominal pain, nausea or vomiting. Lipase and amylase were both normal. A computerized tomography scan of the abdomen and pelvis (CT A/P) did not reveal pancreatitis. Diabetes was well controlled (hemoglobin A1C of level 5.2%) with insulin therapy and her thyroid tests were normal. There was no family history of dyslipidemia. The patient denied alcohol use or the use of other drugs associated with HTG such as estrogen therapy. Based on this and the temporal association, we concluded that PEG caused HTG. Given her asymptomatic presentation, she was managed with a low-fat diet, fenofibrate and omega-3 fish oil. She was also continued on insulin therapy. The patient has since continued chemotherapy without PEG and TG has returned to baseline.

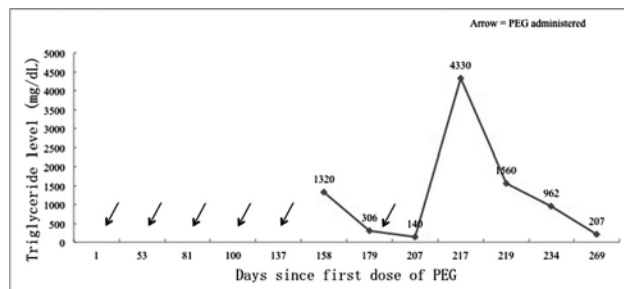


Figure 1. Disease course in patient # 1. Relationship between PEG administration and TG levels.

Patient 2 is a 32-year-old obese (BMI 31 kg/m²) man with ALL admitted with neutropenic fever and methotrexate-induced acute kidney injury. Incidentally, he was found to have severe HTG: TG 4,420 mg/dL. The admission occurred 3 weeks after the fourth PEG dose. His chemotherapy regimen included vincristine, cytarabine, doxorubicin, 6-mercaptopurine, methotrexate, clorafabine and PEG-ASP. He had no personal or family history of dyslipidemia, diabetes or thyroid disorders. As seen in patient 1, there was no clinical evidence of pancreatitis: Lipase and amylase were normal

and CT A/P did not show pancreatitis. Fasting glucose levels ranged between 72 – 116 mg/dL and hemoglobin A1C was 6.6%. Review of his previous drug history was not contributory. A low-fat diet was initiated and PEG was discontinued. Insulin therapy was not started given his glucose levels. Coincidentally, he was receiving heparin infusion – an alternative HTG therapy – for an acute deep vein thrombosis. TG level decreased in four days. Based on this and the temporal association, we concluded that PEG induced HTG. Three weeks later, the patient was re-challenged and received PEG at a half dose. He also received fibrate therapy after AKI resolved. Six months after discharge, TG level was 835 mg/dL which was attributed to medication non-adherence. Nonetheless, TG normalized (75 mg/dL) in 4 months while he was continued on a fibrate (Figure 2).

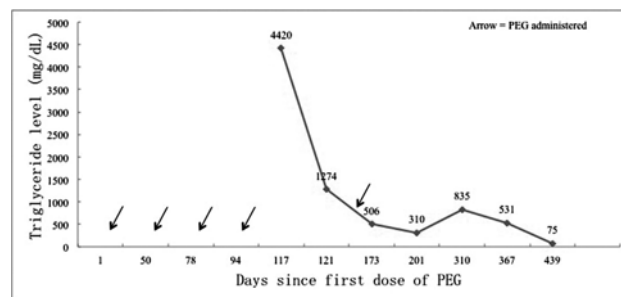


Figure 2. Disease course in patient # 2. Relationship between PEG administration and TG levels.

Literature review

Our PubMed search revealed only eight studies of adults with PEG-induced HTG (Table 1). A total of six were included in our analysis and two (6,7) were excluded, as the authors did not provide specific details of the disease course. Ages ranged from 18 to 53 years, with a mean age of 33.8 years. The chemotherapy regimens included prednisone, dexamethasone and prednisolone along with asparaginase/PEG. Severe hypertriglyceridemia was evident in all patients, with TG ranging from 1,742 to > 13,000 mg/dL. All patient showed decreased TG levels after starting different therapies.

DISCUSSION

Here we report the two adult patients with metabolic risk factors who presented with severe HTG after several doses of PEG. PEG-induced HTG has been previously reported but mainly in the pediatric literature with just few reports in adults (6-13) (Table 1). Parsons and cols. reported a peak TG level of 465 mg/dL during

ASP therapy and a 19% incidence of severe HTG (TG > 1,000 mg/dL) in children treated with ASP (5). In the largest study of children with ALL treated with PEG (prospective observational), the HTG incidence was 7% (n: 18/257). Most episodes of HTG occurred within 2 weeks of steroids and PEG administration, as seen in our patients. Older age (> 10 years) and higher cumulative doses of dexamethasone and PEG were found to be significant risk factors (2). In a study of 40 adults treated with L-ASP, the overall incidence of HTG was 12.5% (n: 5/40). In patients older than 40 years of age, HTG was seen in 21% (n: 3/14) compared to 8% in those younger (n: 2/26) (7).

Most studies have demonstrated a transient and asymptomatic course without pancreatitis, even in patients with severe HTG (TG > 1,000 mg/dL) (4) – a well-recognized cause of pancreatitis (2,14,15). In a series of 38 children, Parson and cols. reported only 4 cases (10.5%) of pancreatitis but none of the patients had a TG > 400 mg/dL. In addition, none of those patients with TG greater than 1000 mg/dL (n: 7/38) developed pancreatitis (5). Overall, pancreatitis is uncommon and affects < 10% of adults treated with PEG (3). Rare, but more severe, complications of ASP-induced HTG have also been reported such as: hyperviscosity syndrome, thrombo-embolism, osteonecrosis, transaminitis and lipemia retinalis (2). The disease course in our patients was similar to that of prior reports: asymptomatic with TG returning to baseline after stopping PEG and while on TG treatment.

The proposed mechanisms of ASP-induced HTG are decreased lipoprotein lipase activity (15), which may result in elevated exogenous chylomicrons (16), and increased endogenous very-low-density lipopro-

tein (VLDL) synthesis (5). Additionally, it's been suggested that ASP may cause a disturbance in lipoprotein metabolism (17).

Whether glucocorticoids (GC), commonly used in ALL's chemotherapy regimens, or ASP are responsible for the TG elevation has been debatable. Steroids also induce VLDL production in the liver; yet they also increase LPL activity, with may be sufficient enough to prevent severe HTG (15). In the study by Cremer and cols., one group received a protocol in which they were administered prednisone and ASP together. These patients showed a significant increase of total cholesterol, TG and chylomicrons. A second group received ASP monotherapy after receiving prednisone. The latter showed a significant increase of TG and chylomicrons but not of total cholesterol. The authors concluded that ASP was responsible exclusively for the increase of TG, likely by the enrichment of exogenous chylomicrons (16). Furthermore, Parson reported an elevation of TG mainly due to endogenous VLDL production during ASP therapy and increased cholesterol while receiving steroids (5).

Huang and cols. suggested that overexpression of ApoE causes HTG in human and mice by a similar mechanism than that of ASP: increasing VLDL synthesis and decreased LPL-mediated VLDL lipolysis. Furthermore, these authors found that the inhibition of lipolysis was related to decreased ApoC-II – a well-known LPL activator (18). Tozuka and cols. studied this specific phenomenon in children with ASP-induced HTG (patients also received prednisolone and vincristine). These authors found that children who had extreme HTG had a higher frequency of ApoE4/E3 phenotype compared to controls, suggesting the

Table 1. Cases of adult patients with PEG-induced HTG undergoing chemotherapy for ALL

Author	Year	Age (years)	Sex	Drug	TG Peak (mg/dL)	Time to peak TG (days)	Treatment
Keung* and cols.	1999	18	M	ASP	1,742	14	Conservative
Nakagawa and cols.	2008	21	M	ASP	9,226	17	Low-fat diet, plasmapheresis, fibrates
Kfoury-Baz* and cols.	2008	34	M	L-ASP	5,620	5	Plasmapheresis
Singh and cols.	2009	42	M	L-ASP	> 13,000	30	Insulin, statin
Konig and Malek	2012	27	F	PEG	> 2,000	21	Low-fat diet, insulin, omega-3
Seah [†] and cols.	2012	53	M	L-ASP	3,552	After 20 th dose of L-ASP	Fasting, fibrates, omega-3
Patient 1	2014	44	F	PEG	4,330	3	Low fat diet, fibrates, omega-3
Patient 2	2014	32	M	PEG	4,420	21	Low-fat diet, heparin infusion

M: male; F: female; L-ASP: asparaginase; PEG: pegylated asparaginase.

*: Patients with pancreatitis.

[†]: Patient with prior history of dyslipidemia on fibrates and statins.

implication of the ApoE4 isoform more specifically. These effects may have been mediated by an inhibitory effect of LPL due to an increase in the ratio of ApoC-III/C-II (17).

Based on available studies and our patients' course, we concluded that patients with metabolic risk factors (obesity, diabetes) are at higher risk for HTG after exposure to steroids and/or PEG. In these cases, the excess VLDL production and increased chylomicrons – induced by steroids and/or PEG, either as sequential or combined therapy – plus ASP-induced decreased LPL activity, will overcome the compensatory effect of GC-induced LPL activity. Thus, an increased TG-rich lipoproteins production associated with decreased clearance will result in HTG. These effects may be due to increase Apo-E4 and decrease Apo-CII isoforms.

Preventing complications in patients with ALL is an important part of the management. As seen in our cases, patients at high risk: those with obesity or diabetes should be carefully monitored for the appearance of HTG. We suggest checking baseline TG levels before starting ASP or PEG or during therapy in these patients. In cases of severe HTG (TG > 1,000 mg/dL), it is suggested to hold ASP/PEG (3). Asparaginase levels normalize in 2-3 weeks after PEG and 2-3 days after ASP. Close monitoring for spontaneous resolution – as previously described – can be attempted in mild or moderate HTG cases (19). Re-challenging with ASP/PEG has been shown to be well tolerated, but this decision should be made on a case-by-case basis and when TGs have normalized (3,19). Immediate dietary modifications and drug therapy is recommended for severe HTG (TG > 1,000 mg/dL) to prevent pancreatitis (4).

Dietary interventions should always be considered as first line therapy for HTG. In acute settings, fasting was shown to increase the effectiveness of drug therapies (20). Decreasing total fat (< 10-15% of total calories) and preferring complex carbohydrates, rich in dietary fiber, is recommended (4).

Drugs for long-term management include: fibrates – considered as first-line drug –, omega-3 fatty acids, or niacin (4). In a case series by Therrien and cols., an overall TG reduction of 31% was noticed in children treated with fenofibrate for HTG secondary to ASP (21). Lashkari and cols. reported four children treated with statins for ASP-induced HTG. The authors ques-

tioned its benefits as some patients may have showed TG normalization with just observation (19).

In cases of severe HTG or HTG-induced pancreatitis, in which an immediate decrease in TG is needed, insulin infusion should be considered – particularly if accompanied by hyperglycemia (20). Insulin activates lipoprotein lipase (LPL) leading to chylomicron degradation, thus increasing TG clearance. In HTG patients treated with insulin infusion, a mean TG reduction of 40% was reported within the first 24 hours. But in those patients that were fasting and treated with insulin infusion, the TG reduction was 87% (20). Cancer patients receiving chemotherapy usually have poor nutritional status and oral intake. We recommend careful monitoring in patients with normoglycemia given their higher risk for hypoglycemia. Heparin infusion can also be used to increase endothelial LPL release. Its use is less favorable than insulin as its effect on LPL is transient. Heparin infusion is indicated in patients with thrombosis and may help to improve the transient ASP-induced HTG state (19). Plasmapheresis is another costlier option that has also been successfully used in patients with severe HTG (TG > 2,000 mg/dL) and HTG-induced pancreatitis (9,11). Our study is limited by its retrospective nature. We only report two patients, with metabolic risk factors, and did not compare with controls. The literature review showed limited evidence in adults. As seen in other cases, patients who develop PEG-induced HTG tend to be asymptomatic and respond to conventional therapies for HTG as well as discontinuation of PEG.

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