CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE	3. SEX	3a. WEIGHT	4-6 REACTION ONSET Day	Month	Year
PRIVACY	UNITED STATES		PRIVACY		Unk	Female	Unk		Unk	

7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)
Event Verbatim [LOWER LEVEL TERM] (Related symptoms if any separated by commas)

Other Serious Criteria: Medically Significant
sirolimus had to be eventually discontinued due to the development of pancreatitis [Pancreatitis]

Case Description: This is a literature report for the following literature source(s): "Orthotopic liver transplant for multifocal lymphangioendotheliomatosis with thrombocytopenia", Pediatr Transplant, 2016; Vol:20, pgs:456-459, DOI:10.1111/petr.12696.

Multifocal lymphangioendotheliomatosis with thrombocytopenia (MLT) is a

(Continued on Additional Information Page)

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION
- ☐ INVOLVED PERSISTENT OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)
#1) Sirolimus (SIROLIMUS) Unknown

(Continued on Additional Information Page)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA

15. DAILY DOSE(S)
#1) 0.01 mg/kg, daily

16. ROUTE(S) OF ADMINISTRATION
#1) Unknown

17. INDICATION(S) FOR USE
#1) multifocal lymphangioendotheliomatosis

(Continued on Additional Information Page)

21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☒ NA

18. THERAPY DATES(from/to)
#1) Unknown

19. THERAPY DURATION
#1) Unknown

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY. (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	
Unknown	Relevant Med History	Thrombocytopenia (Thrombocytopenia)

(Continued on Additional Information Page)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
Pfizer Inc
Pfizer, Inc. 100 Route 206 North
Peapack, NJ 07977 UNITED STATES

26. REMARKS
Receipt Date: 03-JUL-2024 - Safety Receipt Date: 03-JUL-2024

24b. MFR CONTROL NO.
PV202400088483

25b. NAME AND ADDRESS OF REPORTER
NAME AND ADDRESS WITHHELD.

24c. DATE RECEIVED BY MANUFACTURER
03-JUL-2024

24d. REPORT SOURCE
☐ STUDY ☒ LITERATURE ☒ HEALTH PROFESSIONAL ☐ OTHER:

DATE OF THIS REPORT
08-JUL-2024

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOWUP:

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

rare congenital disease, usually presenting with multifocal cutaneous and GI tract vascular lesions and thrombocytopenia. Histologically, these lesions appear to be dilated thin-walled lymphatic vessels, and lesions in the GI tract may result in life-threatening bleeding during the first few weeks of life. Treatment for MLT is challenging. Thrombocytopenia may not respond to platelet transfusions, and medications including corticosteroids, thalidomide, interferon a-2a, and vincristine might not achieve sustained improvement in controlling bleeding. APC also has limited efficacy. Here, the authors report on a girl with MLT who underwent OLT, and whose extrahepatic lesions and thrombocytopenia resolved after transplantation.
Clinical course: An eight-yr-old Hispanic female with a history of MLT, who had previously been reported as the youngest known patient with MLT, was transferred to our institution for possible MVT. She had initially presented at eight days of life with severe hematemesis, hematochezia, and thrombocytopenia. Four days later, multiple erythematous, red-brown, flat papules (ranging from 3 to 8 mm in greatest dimension) began to appear on the back and extremities. Endoscopy was significant for multiple hemangiomatous lesions with hemorrhagic mucosa in the stomach. During infancy, she had been managed with vincristine and methylprednisolone along with supportive care, with her skin lesions completely resolving. However, her gastric lesions persisted, and she required supportive care with multiple transfusions of packed red blood cells, platelets, and fresh frozen plasma, with these transfusions occurring at least monthly and often weekly. She also received recombinant factor VIIa, vitamin K, and aminocaproic acid and frequently underwent endoscopies for APC to treat her bleeding. About a month prior to presentation to their institution, she acutely developed ascites and portal hypertension and was found to have liver involvement by biopsy. She received the angiogenesis inhibitor bevacizumab along with spironolactone, furosemide, and propranolol as an outpatient locally. Despite these treatments, she developed increasing ascites, continued epistaxis, and worsening thrombocytopenia, along with dyspnea and later hematemesis requiring intubation. On arrival, physical examination was significant for scleral icterus, periorbital edema, and significant ascites with marked abdominal distension. Laboratory results were hemoglobin 8.3 g/dL, platelets 56 K/uL, albumin 3 g/dL, total bilirubin 1.5 mg/dL, prothrombin time 15.4 s, INR 1.5, and D-dimer >35 mg/L; normal values included AST 39 U/L, ALT 22 U/L, alkaline phosphatase 83 U/L, GGT 44 U/L, partial thromboplastin time 28 s, and fibrinogen level 388 mg/dL. Transjugular liver biopsy with pressure monitoring confirmed the presence of portal hypertension. However, there was insufficient liver tissue for evaluation. Slides from the outside liver biopsy were re-reviewed, and the original diagnosis of lymphangioendothelioma was confirmed. Endoscopy revealed esophageal varices, for which she received sclerotherapy, along with the previously seen lesions in her stomach; however, it also revealed 2-3 lesions in her duodenum and proximal jejunum, along with multiple lesions throughout her entire colon. Given that despite her portal hypertension, her liver function was relatively stable, the decision was made to stabilize the patient by treating her Kasabach-Merritt-like coagulopathy prior to undergoing MVT. She received 2 mg/kg/day of methylprednisolone, later transitioning to 0.01 mg/kg/day of sirolimus. However, although her coagulation factors normalized, she never developed sustained improvement in her thrombocytopenia and continued to pass blood in her stools despite several weeks of therapy, and sirolimus had to be eventually discontinued due to the development of pancreatitis. Furthermore, her liver function continued to deteriorate, and she developed hepatorenal syndrome, requiring continuous venovenous hemofiltration. Given her tenuous clinical status, her rapidly deteriorating liver function, and the fact that outcomes from OLT are superior to those of MVT, the patient underwent OLT. The explanted liver showed diffuse variably sized hemorrhagic cystic lesions, which were not zone specific, filled with red blood cells, fibrin, and debris, with some showing linear calcification. However, there were no definite lining cells, or viable capillary or lymphatic structures seen within these lesions. CD31, CD34, and D2-40 immunostainings were all negative in those cystic lesions. Diffuse marked cholestasis was present. Trichrome stain showed diffuse severe fibrosis and multifocal regenerative nodules. After OLT, the patient's liver function normalized and thrombocytopenia resolved, and surprisingly, repeat endoscopy performed three months after transplant was negative for any GI lesions. She was discharged on maintenance prednisone 0.15 mg/kg/day and tacrolimus 0.15 mg/kg/day. At latest follow-up 18 months after transplant she has been doing very well, without further episodes of bleeding and platelet levels within normal limits. Repeat capsule endoscopies last done 18 months posttransplant continue to remain negative for GI lesions.
Discussion: The skin lesions are usually multifocal and variable in their appearance and have been described as telangiectatic macules, non-compressible blue/violet plaques and macules, or even large disfiguring tumors. Multiple other organs besides the skin and GI tract may be involved, including the lungs, synovium, muscles, bones, bone marrow, spleen, and brain. The diagnosis of MLT is usually confirmed via skin biopsy, with histological findings of thin-walled dilated vessels in the reticular dermis and subcutis, which are lined with hobnailed endothelial cells and have intraluminal papillary projections. Lymphovascular markers such as CD31, CD34, D2-40, and LYVE1 stain the tumor cells. The histological findings of the explanted liver are intriguing, showing diffuse variably sized hemorrhagic cystic lesions without definite viable lymphangioendotheliomatosis, and a review of the literature shows no similar histological findings reported in other diseases. In conjunction with the patient's clinical history, her previous liver biopsy findings, and focal linear calcifications in the cystic lesions, we postulate that the hemorrhagic cystic lesions represent the necrotic phase of lymphangioendotheliomatosis in the liver. Some patients with MLT may present with coagulopathy along with thrombocytopenia, as their patient did. As consumptive coagulopathy is commonly observed in tumors of vascular origin, it has raised questions of whether these tumors are vascular or lymphatic in origin, or possibly both. Treatments targeting vascular proliferation such as thalidomide, however, have not shown sustained improvement, and bevacizumab, an antibody to vascular endothelial growth factor utilized in the treatment of cancers for its inhibition of angiogenesis, has been used with some success in patients with MLT, but unfortunately did not decrease the incidence of bleeding in our patient. Sirolimus, an inhibitor of angiogenesis, including lymphangiogenesis, has also been used in two patients with MLT, but unfortunately our patient developed pancreatitis, a rare but known adverse effect associated with sirolimus in <3% of patients who receive it. It is possible that earlier initiation of bevacizumab and/or sirolimus may have been helpful in the management of her liver disease; however, she had not had any indication of liver disease until her acute development of ascites a month prior to transfer. Furthermore, despite a month of therapy with bevacizumab, her liver disease continued to worsen, and sirolimus unfortunately could not be tolerated in their patient. Propranolol, which has been utilized in the treatment of neonatal hemangiomatosis, has been used in the treatment of MLT, with inconsistent results. Although their patient did receive propranolol as well, it ultimately did not improve her liver failure or her GI bleeding, and she was found to have multiple GI lesions despite prior treatment with propranolol. It is worth noting that one patient who responded well to a combination of propranolol,

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

aminocaproic acid, and prednisolone was not found to have any GI lesions on abdominal imaging, and serial stool guaiac tests were negative. It is possible that propranolol may be more effective in patients with a variant of MLT that does not include GI lesions, but unfortunately this was not the case for their patient. The fact that both her thrombocytopenia and GI lesions resolved after transplant suggests that there may be a vascular component to the lesions seen in MLT, as it is possible the portal hypertension from her liver failure contributed to both consumption of her platelets and exacerbation of her GI lesions, and therefore, resolution of her portal hypertension after OLT may have helped resolve these other two problems as well. The exact mechanism by which the GI lesions resolved after OLT, however, is at this time unclear, especially given that this is the first reported case of OLT being utilized as treatment for liver failure secondary to MLT. It is unlikely that treatment with bevacizumab played a role in the regression of the GI lesions in their patient, as she was found to have her GI lesions on endoscopy after being treated with bevacizumab. The sirolimus is also unlikely to have significantly contributed to the resolution of the GI lesions, as she continued to pass blood in her stools despite being on sirolimus; however, they did not repeat endoscopy after initiation of sirolimus and prior to OLT, as she was too clinically unstable and it was clear her liver function was worsening. Given the lack of consistently successful treatment for MLT, and the devastating morbidity and mortality associated with this disease, there is clearly a need to continue searching for more definitive treatments for MLT. To the best of their knowledge, this is the first documented case where OLT was performed for the management of liver decompensation secondary to MLT. Advances in OLT in the pediatric population have led to graft survival rates of 93% at 30 days in 2011, and 79% at five yr in deceased donor transplants performed in 2007. Based on Organ Procurement and Transplantation Network data as of October 2, 2015, three-yr patient survival rates for pediatric liver transplant ranges from 79.9% to 86.8%. In contrast, the one-yr survival rate after intestinal transplant is around 70%, and multivisceral transplant remains a challenging option. While OLT in itself is a major surgery, its current rate of success especially compared with that of MVT, along with the fact that transplantation in their case resulted in the resolution of not only their patient's liver failure, but also all other manifestations of her disease, bears its consideration as a potential option for other patients with MLT presenting with liver and GI involvement.

Case Comment: Based on data given and known drug safety profile, the event pancreatitis is possibly related to Sirolimus.

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
1		Activated partial thromboplastin time	28 seconds	
2		Alanine aminotransferase	22 IU/l	
3		Aspartate aminotransferase	39 IU/l	
4		Biopsy	found to have liver involvement	
5		Biopsy liver	the presence of portal hypertension	
6		Biopsy liver was confirmed	diagnosis of lymphangioendothelioma	
7		Blood albumin	3 g/dl	
8		Blood alkaline phosphatase	83 IU/l	
9		Blood bilirubin	1.5 mg/dl	
10		Blood fibrinogen	388 mg/dl	
11		Cell marker Negative	all negative	
12		Coagulation factor	normalized	
13		Endoscopy lesions with hemorrhagic mucosa in the stomach	was significant for multiple hemangiomatous	
14		Endoscopy	esophageal varices,	

ADDITIONAL INFORMATION

13. Lab Data

#	Date	Test / Assessment / Notes	Results	Normal High / Low
15		Fibrin D dimer	less than 35 mg/dl	
16		Gamma-glutamyltransferase	44 IU/l	
17		Haemoglobin	8.3 g/dl	
18		International normalised ratio	1.5	
19		Liver function test	continued to deteriorate	
20		Liver function test	was relatively stable	
21		Physical examination and ascites with marked abdominal distension	significant for scleral icterus, periorbital edema	
22		Platelet count	56 x10 3/mm3	
23		Prothrombin time	15.4 seconds	

14-19. SUSPECT DRUG(S) continued

14. SUSPECT DRUG(S) (include generic name)	15. DAILY DOSE(S); 16. ROUTE(S) OF ADMIN	17. INDICATION(S) FOR USE	18. THERAPY DATES (from/to); 19. THERAPY DURATION
#1) Sirolimus (SIROLIMUS) Unknown; Regimen #1	0.01 mg/kg, daily; Unknown	multifocal lymphangioendotheliomatosis with thrombocytopenia (Cutaneovisceral angiomatosis with thrombocytopenia)	Unknown; Unknown

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Relevant Med History	Cutaneovisceral angiomatosis with thrombocytopenia (Cutaneovisceral angiomatosis with thrombocytopenia);
Unknown	Relevant Med History	Hematemesis (Haematemesis);
Unknown	Relevant Med History	Hematochezia (Haematochezia);
Unknown	Relevant Med History	Thrombocytopenia (Thrombocytopenia);
Unknown	Past Drug Event	vincristine (VINCRISTINE); Drug Indication: Cutaneovisceral angiomatosis with thrombocytopenia (Cutaneovisceral angiomatosis with thrombocytopenia), Drug Reaction: Drug ineffective (Drug ineffective)
Unknown	Past Drug Event	methylprednisolone (METHYLPREDNISOLONE); Drug Indication: Cutaneovisceral angiomatosis with thrombocytopenia (Cutaneovisceral angiomatosis with thrombocytopenia), Drug Reaction: Drug ineffective (Drug ineffective)
Unknown	Past Drug Event	aminocaproic acid (AMINOCAPROIC ACID);

ADDITIONAL INFORMATION

23. OTHER RELEVANT HISTORY continued

From/To Dates	Type of History / Notes	Description
Unknown	Past Drug Event	vitamin K (VITAMIN K [VITAMIN K NOS]);
Unknown	Relevant Med History	Ascites (Ascites);
Unknown to Ongoing	Relevant Med History	Portal hypertension (Portal hypertension);
Unknown	Past Drug Event	bevacizumab (BEVACIZUMAB); Drug Indication: Ascites (Ascites), Drug Reaction: Drug ineffective (Drug ineffective)
Unknown	Past Drug Event	spironolactone (SPIRONOLACTONE); Drug Indication: Ascites (Ascites), Drug Reaction: Drug ineffective (Drug ineffective)
Unknown	Past Drug Event	furosemide (FUROSEMIDE); Drug Indication: Ascites (Ascites), Drug Reaction: Drug ineffective (Drug ineffective)
Unknown	Past Drug Event	propranolol (PROPRANOLOL); Drug Indication: Ascites (Ascites), Drug Reaction: Drug ineffective (Drug ineffective)

24d. Report Source Literature
Journal: Pediatr Transplant
Author: Yang, C.
Title: Orthotopic liver transplant for multifocal lymphangioendotheliomatosis with thrombocytopenia
Volume: 20 Year: 2016 Pages: 456-459