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 Years	3. SEX	4-6 REACTION ONSET Day	Month	Year
Unknown	Portugal				66	M			

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data)

CUTANEOUS TUBERCULOSIS (Cutaneous tuberculosis (10011684), Cutaneous tuberculosis (10011684)) - Unknown
Case level outcome :Unknown

This case, derived from a full text scientific literature article, was received on 30-Aug-2019.

This case refers to a patient who experienced the event cutaneous tuberculosis while on therapy with prednisolone and mycophenolate mofetil (company suspect) for an unknown indication.

Case report: A 66-year-old, white man received a renal transplant from a deceased donor in November 2017 owing to chronic kidney disease (chronic pyelonephritis). Before the transplantation, he was on hemodialysis since 2014. The patient received thymoglobulin to induce immunosuppression, and the current

Cont...

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING
- ☐ CONGENITAL ANOMALY
- ☒ OTHER MEDICALLY IMPORTANT CONDITION

II.SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

1) Prednisolone(Prednisolone)
2) Mycophenolate Mofetil, USP(Mycophenolate Mofetil, USP)

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

15. DAILY DOSE(S)
1) Unknown 2) Unknown

16. ROUTE(S) OF ADMINISTRATION
1) 2)

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

17. INDICATION(S) FOR USE
1) IMMUNOSUPPRESSANT THERAPY[10054980 - Immunosuppressant drug therapy]
2) IMMUNOSUPPRESSANT THERAPY[10054980 - Immunosuppressant drug therapy]

18. THERAPY DATES(from/to)
1) 2)

19. THERAPY DURATION
1) 2)

III.CONCOMITANT DRUG(S) AND HISTORY

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

Tacrolimus(Tacrolimus) Unknown
Thymoglobulin(Thymoglobulin) Unknown

Cont...

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

Past Disease:
RENAL TRANSPLANT[10038533 - Renal transplant]: in November 2017
HEMODIALYSIS[10019480 - Hemodialysis]: since 2014

Cont...

IV.MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

VistaPharm, Inc.
Pharmacovigilance
7265 Ulmerton Road, Largo
Florida (FL) 33771 United States of America

24b. MFR. CONTROL NO.
VER201909-000971(0)

24c. DATE RECEIVED BY MANUFACTURER
30/AUG/2019

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

DATE OF THIS REPORT
21/AUG/2020

25a. REPORT TYPE
☒ INITIAL ☐ FOLLOW UP

Literature Data :

Coelho I, Romaozinho C, Teixeira A, Rodrigues L, Ferreira E, Santos L. A Rare Manifestation of Tuberculosis in a Renal Transplant Patient: A Case Report. Transplant Proc. 2019; 51: 1618-20.

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Cont... = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No. :VER201909-000971(0)**

Describe Reaction(s)(Include relevant test/lab data) (Cont...)

immunosuppression scheme included tacrolimus, mycophenolate mofetil, and prednisolone. The patient had no personal or family history of pulmonary tuberculosis. Six months after surgery, he presented to the emergency department with 2 cutaneous lesions, localized on his back and abdomen, that appeared to be firm, painful, subcutaneous, erythematous nodules with an approximately 5 cm diameter overlying an infected focus and purulent material inside. The patient also had a fever, fatigue, anorexia, and an occasional nonproductive cough. On physical examination, vital signs were within normal limits, the skin demonstrated no other significant changes, and the patient had no notable lymphadenopathy.

Blood analysis showed pancytopenia with an elevation of inflammatory markers and graft dysfunction. We performed tissue cultures and skin biopsy with histological analysis. The patient scored positive with the QuantiFERON-TB Gold test (QFT-Plus; Qiagen) (interferon gamma values of 8.87 IU/mL and 8.97 IU/mL for Mycobacterium tuberculosis specific antigen and mitogen, respectively), raising the suspicion of a TB infection. Histopathology of the lesion showed a nonspecific inflammatory infiltrate, without granulomas, and acid-fast bacillus staining was negative, but polymerase chain reaction (PCR) confirmed the presence of M tuberculosis , which confirmed the diagnosis of cutaneous tuberculosis . The isolated M tuberculosis was later found to be susceptible to all the first-line antimycobacterial drugs. The patient was transferred to the infectious diseases unit and hospitalized in respiratory isolation. Further investigation with a chest computed tomography scan showed multiple lung micronodules in all lung fields. There was also thickening of the interlobular septa, particularly evident in the lower right lobe. The distribution of the micronodulation seemed to be of the random type, suggesting a miliary tuberculosis lung pattern. Microbiological examination (acid-fast bacillus staining, culture, and genome detection) for mycobacteria was conducted also on urine, blood, and bronchoalveolar lavage with positive results.

The patient was treated with a multidrug TB therapy (pyrazinamide, rifampin, ethambutol, and isoniazid) in doses adjusted to the renal function, resulting in cutaneous lesion clearance after 3 weeks. The immunosuppressive therapeutic was adjusted, given the state of severe immunosuppression of the patient. However, the patient suffered progressive worsening of graft function, with an extended hospitalization marked by a pancytopenia of very difficult resolution. Finally, the patient developed graft failure and returned to the hemodialysis. During all the course of the disease, pulmonary symptoms were always mild (occasional nonproductive cough) and resolved after the beginning of TB therapy.

Author’s comment: This case emphasizes a rare cutaneous manifestation with a hematogenous dissemination of M tuberculosis that can develop in immunocompromised patients. Despite the severity of pulmonary involvement with a miliary tuberculosis lung pattern, the patient had only mild respiratory symptoms, and this diagnosis was made after the rare presentation of cutaneous tuberculosis. M tuberculosis infection should al- ways be considered in the differential diagnosis of atypical skin lesions suggestive of an underlying infectious etiology.

Literature citation: Coelho ID, Romaozinho AC, Teixeira AC, Rodrigues L, Ferreira E, Santos L, et al. A Rare Manifestation of Tuberculosis in a Renal Transplant Patient: A Case Report. Transplant Proc. 2019;51:1618-20.

Company's comment: Due to temporal relationship between administration of prednisolone, mycophenolate mofetil and onset of the event "cutaneous tuberculosis" the World Health Organization (WHO) causality to prednisolone and mycophenolate mofetil is possible.

Company Remarks (Sender's comments) (Cont...)

Company's comment: Due to temporal relationship between administration of prednisolone, mycophenolate mofetil and onset of the event "cutaneous tuberculosis" the World Health Organization (WHO) causality to prednisolone and mycophenolate mofetil is possible.

Suspect Drugs (Cont...)

Product-Reaction level

Seq.No. : 1
Drug : Prednisolone(Prednisolone)

Causality

1) CUTANEOUS TUBERCULOSIS (Cutaneous tuberculosis (10011684), Cutaneous tuberculosis (10011684))

Action(s) taken with drug	: Unknown
Outcome after Change in dose	: Not applicable
Outcome after reintro. of dose	: Not applicable
Causality as per reporter (Drug/Vaccine)	: Possible
Causality as per Mfr.(Drug/Vaccine)	: Possible
Dechallenge	: N/A
Rechallenge	: UNK

Seq.No. : 2
Drug : Mycophenolate Mofetil, USP(Mycophenolate Mofetil, USP)

Causality

1) CUTANEOUS TUBERCULOSIS (Cutaneous tuberculosis (10011684), Cutaneous tuberculosis (10011684))

Action(s) taken with drug	: Unknown
Outcome after Change in dose	: Not applicable
Outcome after reintro. of dose	: Not applicable
Causality as per reporter (Drug/Vaccine)	: Possible
Causality as per Mfr.(Drug/Vaccine)	: Possible
Dechallenge	: N/A
Rechallenge	: UNK

Concomitant drugs (Cont...)

Seq.No. : 1

Continuation Sheet for CIOMS report **Mfr. Control No. :VER201909-000971(0)**

Drug : Tacrolimus(Tacrolimus)
Indication for use : 1) IMMUNOSUPPRESSANT THERAPY[10054980 - Immunosuppressant drug therapy]

Seq.No. : 2
Drug : Thymoglobulin(Thymoglobulin)
Indication for use : 1) IMMUNOSUPPRESSANT THERAPY[10054980 - Immunosuppressant drug therapy]

Other relevant history (Cont...)

Concurrent Disease:
CHRONIC PYELONEPHRITIS[10009116 - Chronic pyelonephritis]
OCCASIONAL NONPRODUCTIVE COUGH[10011229 - Cough nonproductive]
ANOREXIA[10002646 - Anorexia]
FATIGUE[10016256 - Fatigue]

Additional information (continuation)

Laboratory data :

Physical Examination: Vital signs were within normal limits, the skin demonstrated no other significant changes, and the patient had no notable lymphadenopathy.

Blood Test: Pancytopenia with an elevation of inflammatory markers and graft dysfunction.

Microbiology Test: Microbiological examination (acid-fast bacillus staining, culture, and genome detection) for mycobacteria was conducted also on urine, blood, and bronchoalveolar lavage with positive results.

Histopathology of the lesion showed a nonspecific inflammatory infiltrate, without granulomas, and acid-fast bacillus staining was negative.

Polymerase chain reaction (PCR) confirmed the presence of M tuberculosis , which confirmed the diagnosis of cutaneous tuberculosis.

The patient scored positive with the QuantiFERON-TB Gold test (QFT-Plus; Qiagen) (interferon gamma values of 8.87 IU/mL and 8.97 IU/mL for Mycobacterium tuberculosis specific antigen and mitogen, respectively), raising the suspicion of a TB infection.

Lab Result :

Test name	Test date	Test result	Normal value	Classification
ACID FAST BACILLUS CULTURE		Negative		
BLOOD TEST		See Rel Lab Tests/Data		
CT SCAN		Multiple lung micronodules in all lung fields.		
HISTOLOGY		see relevant lab test or data		
MICROBIOLOGY TEST		See Rel Lab Tests/Data		
PHYSICAL EXAMINATION		See Rel Lab Tests/Data		
POLYMERASE CHAIN REACTION		see relevant lab test or data		