Response letter answering reviewers

M1 page 1- for manuscript submitted by non-native speakers of English:

Response: Zaki K *et al*. Lymphangioleiomyomatosis recurrence post-transplant

M2-page 1- Author names and institutions

Response: Khawaja S Zaki, Zahra Aryan, Atul, Olufemi Akindipe, Marie Budev,

Respiratory Institute, Cleveland Clinic, Cleveland, Ohio 44195 , United States

M3 page 2 - Author contributions

Response: All authors contributed to acquisition of data, writing and revision of the manuscript.

M4- page 2- Institutional review board statement

Response: This is a single case report and hence no institutional review board statement is required.

M5 – page 2 – Informed consent statement

Response: Verbal consent obtained from the deceased patient's daughter.

M6 – page 2 – Conflict of interest statement

Response: We have no financial relationship to disclose.

M7 – page 4 – Core tip

Response: Core tip - Lymphangioleiomyomatosis (LAM) is a rare, slowly progressive lethal lung disease characterized by proliferation of abnormal smooth muscle cells that targets the lung, causing cystic destruction and eventual respiratory failure and death. mTOR inhibitors such as sirolimus has shown promise in stabilization of lung function. Lung transplant is a viable option in patient whose lung function continues to decline despite of mTOR inhibitors. However recurrence of LAM in transplanted lung has been reported. We describe a case of LAM recurrence in a double lung transplant recipient nine years after transplantation, our therapeutic approach once recurrence documented with review of literature.

M8 – page 5 – Please put reference numbers in square brackets

Response: Reference numbers in put in square brackets in superscript.

M9 – page 7 – No figure 2, please check

Response: Figures numbered as Figure 1 and Figure 2

Page 10 – Following sections included:

COMMENTS

Case characteristics

A 66 year of women post double lung transplantation for Lymphangioleiomyomatosis (LAM) presented with dyspnea on exertions after 9 years post transplantation.

Clinical diagnosis

Her clinical examination remained unremarkable and hasn't change since prior visits.

Differential diagnosis

Infections in immunocompromise host, acute rejection, chronic rejection like Bronchiolitis Obliterans Syndrome (BOS).

Laboratory diagnosis

All laboratory work up was in normal limits.

Imaging diagnosis

Chest X-ray showed chronic right upper lobe interstitial and nodular changes. CT of the chest showed right upper lobe nodules with bilateral interstitial thickening and scattered ground glass opacities which were unchanged from prior studies.

Pathological diagnosis

Histopathological examination of the Transbronchial Biopsy revealing spindle shaped LAM cells without evidence of infection or rejection suggestive of LAM recurrence.

Treatment

Calcineurin inhibitor immunosuppressive therapy was switched to sirolimus monotherapy but has to be stopped due to surgery. Later again restarted resulted in brief stabilization of lung function. However the patient developed complications of infection and rejection proved to be fatal.

Related reports

Lung transplantation represents one of the most effective and acceptable therapeutic option for LAM patients with respiratory failure. The recurrence is rare and mostly remains asymptomatic. Sirolimus has shown to stabilized lung function in patients with LAM. However post transplantation its role is not clear.

Term explanation

Broncholitis obliterans syndrome (BOS) is a form of chronic lung allograft dysfunction that commonly presents with obstructive ventilator defect and decline in forced expiratory volume in 1 sec post lung transplantation.

Experiences and lessons

LAM is a rare disease and its recurrence post lung transplantation is even rarer. Sirolimus therapy slows the progression of disease in patient with LAM. Our clinical acumen supports the notion that in lung transplant recipients with LAM, sirolimus should be considered as a primary anti-rejection medication either as monotherapy or as dual therapy with a calcineurin inhibitors

M10 – page 11 – Please delete et al, and list all author's names

Response – changes applies

M11 – page 11 – Please add PubMed citation numbers and DOI citations to the reference list and list all authors.

Response – PMID and DOI citations included.

Reviewer's comments to authors:

Is medical therapy alone can replace or delay the option of lung transplant? Is there a need for patient post-transplant to be on mTOR inhibitors? if yes for how long? What are the factors to decide between re-transplant or medical treatment?

Response:

Theoretically, therapy with mTOR inhibitors is likely to delay the progression or recurrence of LAM. However, there are no randomized trials to support the recommendation due to the rarity of the disease and its presentations. It is advisable to place the patients on lifelong mTOR inhibitors following the lung transplantation to delay the recurrence of LAM in the allograft. Intolerance or complications of mTOR inhibitors may limit their use in some patients, who may then require re-transplantation.