

Dear Editors:

Name of Journal: World Journal of Clinical Cases

Manuscript NO: 54535

Title: Tuberous Sclerosis Complex Presenting as Primary Intestinal Lymphangiectasia: A case report

We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in yellow in the paper. The language editing is highlighted in green. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Reviewer #1 (code: 03726743)

1. Response to comment: Title: -The comma should be removed.

Response: We have made correction according to the Reviewer's comments.

2. Response to comment: Abstract: - "We observed that PIL and tuberous sclerosis complex (TSC) have common clinical manifestations and downstream pathways." makes it seem like the authors have significantly studied this entity; may want to revise the wording if this statement is based solely on this one patient. Similarly, "Therefore, this paper holds that PIL is a clinical manifestation of TSC." seems a bit overstated/should be softened.

Response: It is really true as Reviewer suggested that the statement is not properly expressed. We have revised all the similar sentences in the text.

Line 14-16, the statements of "We observed that PIL and tuberous sclerosis complex (TSC) have common clinical manifestations and downstream pathways." were corrected as "Through a literature review, we found that PIL and tuberous sclerosis complex (TSC) have some common symptoms and molecular pathways."

Line 29-31, the statements of "Therefore, this paper holds that PIL is a clinical manifestation of TSC." were corrected as "In summary, when patients with hypomelanotic macules or enamel hypoplasia are diagnosed with PIL, TSC

gene screening may be important for further diagnosis.”

Line 44, the statements of “These findings suggest that PIL may be a manifestation of TSC.” were corrected as “These findings suggest that PIL may be a manifestation of TSC in some cases.”

Line 189-192, the statements of “IL is a clinical manifestation of TSC, which may be caused by the abnormal activation of *mTOR* after *TSC1/TSC2* mutation, resulting in intestinal lymphatic hyperplasia, lymphangiectasia, and finally poor reflux of tissue fluid.” were corrected as “In this patient, PIL appears to be a clinical manifestation of TSC and may be caused by abnormal activation of mTOR after *TSC1* mutation, resulting in intestinal lymphatic hyperplasia, lymphangiectasia, and finally poor efflux of tissue fluid.”

3. Response to comment: -What is the imaging that the authors are referring to here: “...we arranged an imaging examination and TSC gene examination for the patient.” Would specify, or perhaps state “multiple imaging examinations were performed, as was TSC gene analysis” (or similar).

Response: We have made correction according to the Reviewer’s comments.

Line 22-24, the statements of “In order to evaluate the condition of the child and make a definite diagnosis, we arranged an imaging examination and TSC gene examination for the patient.” were corrected as “To evaluate the condition of the child and make a definite diagnosis, multiple imaging examinations were performed, as was TSC gene analysis.”

4. Response to comment: Core tip: -Needs extensive English language review. Text: - Needs extensive English language review.

Response: Language editing had been done, before submission. The language editing is highlighted in green.

5. Response to comment: “...which affects the living quality of children”; is this meant to say “the quality of life of children”? Also, it should be noted

that PIL is not exclusively a disease of pediatrics.

Response: We are very sorry for our negligence. We have revised all the similar sentences in the text. Line 46-47, the statements of “Primary intestinal lymphangiectasia (PIL) is a kind of protein-losing enteropathy with unknown etiology and no specific treatment, which affects the living quality of children.” were corrected as “Primary intestinal lymphangiectasia (PIL) is a kind of protein-losing enteropathy with unknown etiology and no specific treatment.”

Line 205-206, the statements of “Further investigation in this direction would help us to understand the disease and help children live more fulfilling lives.” were corrected as “Further investigation in this direction would help us to understand the disease and increase patients’ quality of life.”

6. Response to comment: “ protein-loss enteropathy” should probably be “protein-losing enteropathy” -The authors use “PIL” and “IL”; is this intentional, or are they representing the same thing?

Response: “IL” is a clerical error and this article is all about PIL. We are very sorry for our incorrect writing. Line 189, the statements of “IL” were corrected as “PIL” .

7. Response to comment: The discussion is quite lengthy and difficult to follow; please consider revising the organization and transitions.

Response: We have revised the discussion to make the language more concise.

8. Response to comment: Figures: -The hypopigmented regions appear to be larger than “macules”; please revise wording.

Response: As Reviewer suggested that we corrected it as “hypopigmented regions”, in line 22, 52, 85, 94, 311.

Special thanks to you for your good comments.

Reviewer #2 (code: 02476743)

1. Response to comment: Statement of Ethics: In addition to Institutional Review Board approval, authors should also state that subject's parents have given their written informed consent.

Response: As Reviewer suggested that "Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images. This work was approved by the ethics committee of Guangzhou Women and Children's Medical Center." was added in line 216-219.

2. Response to comment: More discussion regarding the medical policy implications of their findings would be essential for the applications in medical decision making.

Response: As Reviewer suggested, "mTOR inhibitors have shown very good prospects in the treatment of vascular malformations, and their side effects are known. If the indications for these drugs expand, they might be better for patients than are currently approved drugs." was added in line 183-187.

3. Response to comment: The authors should add the comments related to selection bias in this study to the perceived limitation subsection.

Response: As Reviewer suggested, "However, selection bias may exist due to the small number of cases. Further studies with large samples of patients with PIL and TSC, allowing minimization of selection bias, are in great need." was added in line 199-201.

4. Response to comment: The references should be simplified.

Response: we have deleted similar references.

Special thanks to you for your good comments.

Other changes after language editing:

1. Line 18-19, the statements of "Here, we present a case with a three-year history of primary intestinal lymphangiectasia." were corrected as "Here, **we present the case of a patient with** a three-year history of primary intestinal lymphangiectasia."
2. Line 19-20, the statements of "This time, the patient came to the hospital again with abdominal distension and swelling of the left leg." were corrected as "**The patient most recently visited the hospital** with abdominal distension and swelling of the left leg."
3. Line 20-22, the statements of "His mother told us she was diagnosed with TSC one year ago, which alerted us, because the patient has multiple pigmentation spots." were corrected as "His mother told us she was diagnosed with TSC one year **previously**, which alerted us because the patient **had multiple regions of pigmentation.**"
4. Line 24, the statements of "The results reached the diagnostic criteria of TSC." were corrected as "The results **met** the diagnostic criteria **for** TSC."
5. Line 25-27, the statements of "Through consulting the literature, it can be seen that changes in the molecular gene level of TSC can lead to abnormal lymphatic vessels." were corrected as "**Through a review of the literature**, it can be seen that changes in the molecular gene level of TSC can lead to abnormal lymphatic vessels."
6. Line 37, the statements of "We present a case with a history of PIL." were corrected as "**We present the case of a patient** with a history of PIL."
7. Line 38-39, the statements of "Only two cases of PIL associated with TSC had been reported at the time of writing this, and this report is the third case." were corrected as "Only two cases of PIL associated with TSC had been reported at the time **of this writing**, and this report **presents** the third case."
8. Line 39-42, the statements of "It has been reported in previous cases that

PIL patients can suffer from hypomelanotic macules or enamel hypoplasia, which are the clinical features of TSC.” were corrected as “It has been reported in previous cases that PIL patients can exhibit hypomelanotic macules or enamel hypoplasia, which are the clinical features of TSC.”

9. Line 42-43, the statements of “Through consulting the literature, it can be seen that changes in the molecular gene level of TSC can lead to abnormal lymphatic vessels.” were corrected as “Through a review of the literature, it can be seen that changes in the molecular gene level of TSC can lead to lymphatic vessels abnormalities.”
10. Line 49-51, the statements of “It has been reported in previous cases that PIL patients can suffer from hypomelanotic macules or enamel hypoplasia, which are the clinical features of tuberous sclerosis complex (TSC).” were corrected as “It has been reported in previous cases that PIL patients can exhibit hypomelanotic macules or enamel hypoplasia, which are the clinical features of tuberous sclerosis complex (TSC).”
11. Line 52-54, the statements of “This time he presented to our department because of abdominal distension and left lower extremity swelling again.” were corrected as “At his most recent visit, he presented to our department because of abdominal distension and left lower extremity swelling.”
12. Line 56-57, the statements of “Only two cases of PIL associated with TSC had been reported at the time of writing this, and this report is the third case.” were corrected as “Only two cases of PIL associated with TSC had been reported at the time of this writing, and this report presents the third case.”
13. Line 60-62, the statements of “Rapamycin has been widely used for TSC or complications with lymphedema, and showed beneficial effects, providing a new idea for the treatment of PIL” were corrected as “Rapamycin has been widely used for TSC or complications with lymphedema and has shown beneficial effects, providing a new idea for the treatment of PIL.”
14. Line 65-66, the statements of “A 5-year-old boy presented with recurrent

abdominal distension and left lower extremity swelling for three years.” were corrected as “A 5-year-old boy presented with recurrent abdominal distension and left lower extremity swelling over a three-year period.”

15. Line 68-70, the statements of “In September 2015, he was diagnosed with PIL because of diarrhea, edema, hypoproteinemia, lymphocytopenia, endoscopic findings, and biopsy (Fig 1).” were corrected as “In September 2015, the patient was diagnosed with PIL because of diarrhea, edema, hypoproteinemia, lymphocytopenia, endoscopic findings, and biopsy findings (Fig 1).”
16. Line 70, the statements of “Normal stool was found under uncontrolled diet.” were corrected as “The stool was found to be normal under an uncontrolled diet.”
17. Line 71-73, the statements of “He experienced intermittent attacks of abdominal distension and swelling of the left lower extremity, more secondary to diarrhea, about 2 times per year.” were corrected as “He experienced intermittent attacks of abdominal distension and swelling of the left lower extremity, primarily secondary to diarrhea, approximately 2 times per year.”
18. Line 73-74, the statements of “After supplementation with albumin and diuresis, swelling was relieved.” were corrected as “After albumin supplementation and diuresis, the swelling was relieved.”
19. Line 74-75, the statements of “Since onset, the patient had had no history of seizures, behavior changes or mood disturbances.” were corrected as “Since the time of onset, the patient had no history of seizures, behavioral changes or mood disturbances.”
20. Line 77-78, the statements of “He had a surgery history of posterior fibrolipoma resection in April 2015.” were corrected as “The patient had a surgical history of posterior fibrolipoma resection in April 2015.”
21. Line 80, the statements of “His language and exercise were normal.” were corrected as “The patient’s language and physical abilities were normal.”
22. Line 80-81, the statements of “He got on well with his classmates at school.”

were corrected as “He interacted appropriately with his classmates at school.”

23. Line 81-83, the statements of “More than one year ago, his mother was diagnosed as TSC because of shagreen patch, pulmonary lymphangiomyomatosis, and *TSC1* mutation (147C>A(p.Tyr49Ter)).” were corrected as “More than one year previously, his mother was diagnosed with TSC because of a shagreen patch, pulmonary lymphangiomyomatosis, and *TSC1* mutation (147C>A (p.Tyr49Ter)).”
24. Line 86-88, the statements of “The abdomen, left scrotum and lower extremity were swollen, which were rubbery to touch and normal skin temperature. The shifting dullness was negative.” were corrected as “The abdomen, left scrotum and lower extremity were swollen and rubbery to the touch and had a normal skin temperature. The patient was negative for shifting dullness.”
25. Line 88-90, the statements of “The abdominal circumference was 70.5cm. The right leg root circumference was 28.5cm, while the left leg root circumference was 42.5cm (Fig 2).” were corrected as “The abdominal circumference was 70.5 cm. The right leg root circumference was 28.5 cm, while the left leg root circumference was 42.5 cm (Fig 2).”
26. Line 90-91, the statements of “His neurological examination was unremarkable.” were corrected as “The patient’s neurological examination was unremarkable.”
27. Line 96-100, the statements of “The mutation of *TSC1* was detected. *TSC1*, c.147C>A(p.Tyr49Ter). c.147C>A(p.Tyr49Ter) is a nonsense mutation, which is the same mutation as his mother’s. The 49th amino acid of the translation product protein changes from Tyr to the termination codon, leading to the early termination of protein translation.” were corrected as “Mutation of *TSC1* was detected; *TSC1*, c.147C>A (p.Tyr49Ter). c.147C>A (p.Tyr49Ter), a nonsense mutation, was the same mutation that the patient’s mother exhibited. The 49th amino acid of the translated protein is changed from Tyr to a termination codon, leading to early termination of protein

translation.”

28. Line 103-104, the statements of “The ultrasound showed multiple solid nodules in the left popliteal fossa.” were corrected as “**Ultrasound** showed multiple solid nodules in the left popliteal fossa.”
29. Line 104-106, the statements of “Abdominal ultrasonography revealed thickening of most intestinal walls and thickening of mesentery with dilatation of veins, and peritoneal effusion.” were corrected as “Abdominal ultrasonography revealed thickening of most intestinal walls, **thickening of the** mesentery with dilatation of veins, and peritoneal effusion.”
30. Line 107-109, the statements of “Echocardiography indicated patent foramen ovale (3.3mm), and lower extremity venous ultrasounds were normal.” were corrected as “Echocardiography indicated **a** patent foramen ovale (**3.3 mm**), and lower extremity venous ultrasounds were normal.”
31. Line 109-112, the statements of “Magnetic resonance imaging (MRI) showed subependymal nodules in anterior of the left lateral ventricle (Fig 3) and enlargement of the left renal parenchyma with abnormal signal.” were corrected as “Magnetic resonance imaging (MRI) showed subependymal nodules **in the anterior region of the** left lateral ventricle (Fig 3) and enlargement of the left renal parenchyma with abnormal signal intensity.”
32. Line 112-114, the statements of “Left kidney and abdominal cavity had effusion. Intestinal wall and mesenteric fat space were generally thickened with edema and abnormal signal, particularly in the left semi-intestinal tube.” were corrected as “**The** left kidney and abdominal cavity had effusion. **The** intestinal wall and mesenteric fat space were generally thickened, with edema and **abnormal signal intensity**, particularly in the left semi-intestinal tube.”
33. Line 116, the statements of “So far, the diagnosis of TSC could be confirmed.” were corrected as “**Thus** far, the diagnosis of TSC could be confirmed.”
34. Line 118-120, the statements of “Symptomatic support treatment was given. After treatment with albumin, diuretic, and calcium supplements, the swelling of the

patient gradually subsided." were corrected as "Supportive symptomatic treatment was given. After treatment with albumin, a diuretic, and calcium supplements, the patient's swelling gradually subsided."

35. Line 122, the statements of "The patient's condition improved and was discharged from hospital." were corrected as "The patient's condition improved, and he was discharged from the hospital."

36. Line 125, the statements of "At present, the etiology is unknown." were corrected as "Currently, the etiology is unknown."

37. Line 126-129, the statements of "Patients need a long-term low-fat and medium-chain fatty acid diet, selective use octreotide and glucocorticoids, and even need surgical resection of the diseased intestinal and lymphoid vessels." were corrected as "Patients need a long-term low-fat and medium-chain fatty acid diet, selective use of octreotide and glucocorticoids, and even surgical resection of the diseased intestinal and lymphoid vessels."

38. Line 130-131, the statements of "The mother of this patient was diagnosed with TSC one year ago, with *TSC1* gene mutation positive (147C>A(p.Tyr49Ter))." were corrected as "The mother of this patient was diagnosed with TSC one year previously and was positive for *TSC1* gene mutation (147C>A (p.Tyr49Ter))."

39. Line 133-136, the statements of "These two genes are located on chromosomes 9 and 16, respectively encoding hamartin and tuberin, forming the TSC1/TSC2 complex to inhibit the *mTOR* signal pathway, and regulating cell growth and function." were corrected as "These two genes are located on chromosomes 9 and 16, encoding hamartin and tuberin, respectively, which form the TSC1/TSC2 complex to inhibit the *mTOR* signaling pathway and regulate cell growth and function."

40. Line 140-141, the statements of "The clinical manifestations of a few TSC patients included lymphedema" were corrected as "The clinical manifestations of TSC include lymphedema in a small number of parents."

41. Line 141-142, the statements of "There have been twelve reports in which most

of the patients had asymmetrical swelling of limbs.” were corrected as “There have been twelve reports in which most of the patients had asymmetrical limb swelling.”

42. Line 142-145, the statements of “Here, we summarize the previously reported cases of TSC with lymphedema in children (supplemental table 2), and found that lower extremity involvement (12/16) and abdominal distension (4/16) were more common.” were corrected as “Here, we summarized the previously reported cases of TSC with lymphedema in children (supplemental table 2) and found that lower extremity involvement (12/16) and abdominal distension (4/16) were more common than other symptoms in these cases.”
43. Line 145-148, the statements of “Six patients were treated with sirolimus or everolimus, of which three were relieved, two were ineffective, and one was discontinued due to severe side effects.” were corrected as “Six patients were treated with sirolimus or everolimus; among which symptoms were relieved in three, treatment was ineffective in two, and treatment was discontinued due to severe side effects in one.”
44. Line 148-149, the statements of “It has been reported that children with TSC have a benign vascular lymphatic malformation” were corrected as “It has been reported that children with TSC have benign vascular lymphatic malformations.”
45. Line 149-152, the statements of “The etiology of lymphedema in these children with TSC is unknown, which may be due to abnormal activation of the *mTOR* signaling pathway, resulting in abnormal lymphatic system structure.” were corrected as “The etiology of lymphedema in these children with TSC is unknown but may be due to abnormal activation of the *mTOR* signaling pathway, resulting in abnormal lymphatic system structure.”
46. Line 153-155, the statements of “The function of lymphatic vessels is to recycle interstitial fluid into blood circulation, which provides the necessary conditions for the maintenance of normal fluid homeostasis, fat absorption, and immune response

in the body.” were corrected as “The function of lymphatic vessels is to recycle interstitial fluid into the blood circulation, thus providing the necessary conditions for the maintenance of normal fluid homeostasis, fat absorption, and immune response in the body.”

47. Line 156-158, the statements of “The walls of most lymphatic vessels are composed of a single layer of lymphatic endothelial cells, which originated from veins in the embryonic stage and gradually migrated to the periphery to form a network distribution” were corrected as “The walls of most lymphatic vessels are composed of a single layer of lymphatic endothelial cells, which originate from veins in the embryonic stage and gradually migrate to the periphery to form a distribution network.”

48. Line 159-160, the statements of “Lymphangiogenesis is under the control of a tightly orchestrated equilibrium between numerous players.” were corrected as “Lymphangiogenesis is under the control of a tightly orchestrated equilibrium among numerous players.”

49. Line 167-169, the statements of “Therefore, *mTOR* is abnormally activated in lymphatic vascular endothelial cells when lymphatic vascular malformation occurs” were corrected as “Therefore, *mTOR* is abnormally activated in lymphatic vascular endothelial cells under conditions of lymphatic vascular malformation”

50. Line 170-172, the statements of “Rapamycin or other *mTOR* inhibitors are widely used in the treatment of vascular malformations, including lymphangiomyomatosis (LAM) in patients with TSC, etc., with excellent therapeutic effects” were corrected as “Rapamycin and other *mTOR* inhibitors are widely used in the treatment of vascular malformations, including lymphangiomyomatosis (LAM) in patients with TSC, etc., with excellent therapeutic effects”

51. Line 173-175, the statements of “In supplemental table 2, six cases of TSC complicated with lymphoid swelling were treated with *mTOR* inhibitor, of which three cases were effective.” were corrected as “Supplemental table 2 describes six cases of TSC complicated with lymphoid swelling that were treated

with an *mTOR* inhibitor, which was effective in three cases.”

52. Line 178-180, the statements of “Rapamycin completely blocks the phosphorylation of *p70S6* kinase, and thus blocks the pathway of action of *VEGF-C/VEGFR-3*, thereby impeding lymphangiogenesis.” were corrected as “Rapamycin completely blocks the phosphorylation of *p70S6* kinase and thus blocks the pathway of *VEGF-C/VEGFR-3* activity, thereby impeding lymphangiogenesis.”
53. Line 180-183, the statements of “Because the administration of rapamycin in children is only approved for renal transplantation and everolimus is only approved for subependymal giant cell astrocytoma in china, we did not administer the drug in this case.” were corrected as “Because administration of rapamycin in children is approved only for renal transplantation and everolimus is approved only for subependymal giant cell astrocytoma in China, we did not administer the drug to this patient.”
54. Line 192-195, the statements of “Therefore, the authors maintain that TSC screening should be routine for the diagnosis of PIL, such as *mTOR* immunohistochemistry for pathological intestinal biopsies and gene examination for blood sampling, to assist in etiological diagnosis.” were corrected as “Therefore, the authors maintain that TSC screening, such as *mTOR* immunohistochemistry of pathological intestinal biopsies and genetic evaluation of blood samples, should be routine for patients diagnosed with PIL to assist in etiological diagnosis.”
55. Line 195-198, the statements of “Especially for patients with hypomelanotic macules, epilepsy, dental enamel pits, or other manifestations, it is strongly suggested that they may have TSC, and active screening is needed to avoid delayed diagnosis and treatment.” were corrected as “Hypomelanotic macules, epilepsy, dental enamel pits, or other manifestations in patients are especially strongly suggestive of TSC, and active screening is needed to avoid delayed diagnosis and treatment.”
56. Line 198-199, the statements of “Etiological diagnosis allows for targeted

treatment strategies, in which rapamycin can be used.” were corrected as “Etiological diagnosis allows for targeted treatment strategies that could include rapamycin.”

57. Line 201-205, the statements of “However, there are other etiologies that lead to PIL, as the regulation of lymphangiogenesis is a complex network. The *mTOR/S6K* signaling pathway is the main downstream pathway of VEGF-C/VEGFR-3, but not the specific one.” were corrected as “There are other etiologies that lead to PIL, as the regulation of lymphangiogenesis is controlled by a complex network. The *mTOR/S6K* signaling pathway is the main downstream pathway of VEGF-C/VEGFR-3 but not the only pathway.”

58. Line 306-309, the statements of “FIGURE 1. (A) Gastroscopy showed that the mucosa of descending segment and horizontal segment of duodenum was rough with dense white spots on the surface, on 09 September 2015. (B) Histological image showing dilated lymph vessels. (hematoxylin and eosin stain $\times 100$)” were corrected as “FIGURE 1. (A) Gastroscopy on 09 September 2015 showed that the mucosa of the descending segment and horizontal segment of the duodenum was rough, with dense white spots on the surface. (B) Histological image showing dilated lymph vessels. (hematoxylin and eosin staining, $\times 100$)”

59. Line 311, the statements of “(A) Multiple hypopigmented macules in the back and buttocks.” were corrected as “(A) Multiple hypopigmented regions on the back and buttocks.”

60. Line 314-315, the statements of “FIGURE 3. Axial MRI (T1 and T2) of the brain, demonstrating subependymal nodules in anterior of the left lateral ventricle.” were corrected as “FIGURE 3. Axial MRI (T1 and T2) of the brain, demonstrating subependymal nodules in the anterior region of the left lateral ventricle.”

Sincerely,

Wen-Hao Lin