Review Form 1.6

Journal Name:	**Asian Journal of Orthopaedic Research**
Manuscript Number:	**Ms_AJORR_76893**
Title of the Manuscript:	**Oncogenic Osteomalacia Secondary to Hemangiopericytoma - a case report**
Type of the Article	**Case study**

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty'**, provided the manuscript is scientifically robust and technically sound.
To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

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PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments		
Minor REVISION comments	I suggest to the authors that in the beginning of the paper to present in 1-2 sentences the purpose of this case report. The following sentences require completion of references: - *This disease was first described by Dr. Rober McCane…..* I suggest adding references to McCance RA. Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. Q J Med. 1947;16:33–46. - *OO had association with syndromes such as neurofibromatosis and McCune-Albright syndrome and in patient with carcinomas.* I suggest to cite and adding references to Bowe, A.E., Finnegan, R., de Beur, S.M.J., Cho, J., Levine, M.A., Kumar, R. and Schiavi, S.C., 2001. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. *Biochemical and biophysical research communications*, *284*(4), pp.977-981. - *It has been reported that OO associated with mesenchymal tumour over expresses FGF-23. This protein inhibits renal tubular epithelial phosphate transport and this is thought to be the mechanism for most cases of OO.* I suggest to cite and adding references to K. E. White, T. E. Larsson, and M. J. Econs, "The roles of specific genes implicated as circulating factors involved in normal and disordered phosphate homeostasis: frizzled related protein-4, matrix extracellular phosphoglycoprotein, and fibroblast growth factor 23," *Endocrine Reviews*, vol. 27, no. 3, pp. 221–241, 2006. - *Weidner and Santa Cruz (1987) coined the term "Phosphaturic Mesenchymal Tumour, Mixed Connective Tissue variant"* I suggest adding references to Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. Cancer. 1987;59:1442–54. - *Prevalence of TIO is not known but till now 300 cases have been reported.* I suggest to see the article • Folpe A.L., Fanburg-Smith J.C., Billings S.D., Bisceglia M., Bertoni F., Cho J.Y. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol.* 2004;28:1–30. • Jiang Y., Xia W.B., Xing X.P., Silva B.C., Li M., Wang O. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature. *J Bone Miner Res.* 2012;27:1967–1975. • Sun Z.J., Jin J., Qiu G.X., Gao P., Liu Y. Surgical treatment of tumor-induced osteomalacia: a retrospective review of 40 cases with extremity tumors. *BMC Musculoskelet Disord.* 2015;16:43. • Jagtap V.S., Sarathi V., Lila A.R., Malhotra G., Sankhe S.S., Bandgar T. Tumor-induced osteomalacia: a single center experience. *Endocr Pract.* 2011;17:177–184. • Endo I., Fukumoto S., Ozono K., Namba N., Inoue D., Okazaki R. Nationwide survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases	-

Comment [i1]: McCance RA. Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. Q J Med. 1947;16:33–46.

Comment [i2]: Bowe, A.E., Finnegan, R., de Beur, S.M.J., Cho, J., Levine, M.A., Kumar, R. and Schiavi, S.C., 2001. FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. *Biochemical and biophysical research communications*, *284*(4), pp.977-981.

Comment [i3R2]: M. K. Drezner, "Tumor-induced osteomalacia," *Reviews in Endocrine and Metabolic Disorders*, vol. 2, no. 2, pp. 175–186, 2001.
K. E. White, T. E. Larsson, and M. J. Econs, "The roles of specific genes implicated as circulating factors involved in normal and disordered phosphate homeostasis: frizzled related protein-4, matrix extracellular phosphoglycoprotein, and fibroblast growth factor 23," *Endocrine Reviews*, vol. 27, no. 3, pp. 221–241, 2006.

Comment [i4]: Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets. Cancer. 1987;59:1442–54.

Comment [i5]: 163 cazuri in Shah, R., Lila, A.R., Jadhav, S., Patil, V.A., Mahajan, A., Sonawane, S., Thadani, P., Dcruz, A.K., Pai, P.S., Bal, M. and Kane, S., 2019. Tumor induced osteomalacia in head and neck region: single center experience and systematic review. *Endocrine connections*, *1*(aop).
About 500 cases of TIO have been reported worldwide
till in 2018.
Folpe A.L., Fanburg-Smith J.C., Billings S.D., Bisceglia M., Bertoni F., Cho J.Y. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol.* 2004;28:1–30. [PubMed] [Google Scholar]
6. Jiang Y., Xia W.B., Xing X.P., Silva B.C., Li M., Wang O. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature. *J Bone Miner Res.* 2012;27:1967–1975. [PubMed] [Google Scholar]
7. Sun Z.J., Jin J., Qiu G.X., Gao P., Liu Y. Surgical treatment of tumor-induced osteomalacia: a retrospective review of 40 cases with extremity tumors. *BMC Musculoskelet Disord.* 2015;16:43. [PMC free article] [PubMed] [Google Scholar]
8. Jagtap V.S., Sarathi V., Lila A.R., Malhotra G., Sankhe S.S., Bandgar T. ...

in Japan: prevalence, biochemical data and treatment. *Endocr J.* 2015;62:811–816.
- Honda R., Kawabata Y., Ito S., Kikuchi F. Phosphaturic mesenchymal tumor, mixed connective tissue type, non-phosphaturic variant: report of a case and review of 32 cases from the Japanese published work. *J Dermatol.* 2014;41:845–849.
- Shah R, Lila AR, Jadhav S, Patil VA, Mahajan A, Sonawane S, Thadani P, Dcruz AK, Pai PS, Bal M, Kane S. Tumor induced osteomalacia in head and neck region: single center experience and systematic review. Endocrine connections. 2019 Sep 1;1(aop).
- Kobayashi H, Ito N, Akiyama T, Okuma T, Kinoshita Y, Ikegami M, Shinoda Y, Fukumoto S, Tanaka S, Kawano H. Prevalence and clinical outcomes of hip fractures and subchondral insufficiency fractures of the femoral head in patients with tumour-induced osteomalacia. International orthopaedics. 2017 Dec;41(12):2597-603.
- Yin Z, Du J, Yu F, Xia W. Tumor-induced osteomalacia. Osteoporosis and sarcopenia. 2018 Dec 1;4(4):119-27.

Over 500 cases of TIO have been reported worldwide till in 2018.

- *Meyer et al and Nebitt et al demonstrated circulating factor that could be responsible in sets of experiments over nice.*

I suggest correct nice – **mice** and adding references to

Meyer RA, Jr, Meyer MH, Gray RW. Parabiosis suggests a humoral factor is involved in X-linked hypophosphatemia in mice. *J Bone Miner Res.* 1989 Aug;**4**(4):493–500.

Meyer RA, Jr, Tenenhouse HS, Meyer MH, Klugerman AH. The renal phosphate transport defect in normal mice parabiosed to X-linked hypophosphatemic mice persists after parathyroidectomy. *J Bone Miner Res.* 1989 Aug;**4**(4):523–532. [

Nesbitt, T., Coffman, T.M., Griffiths, R. and Drezner, M.K., 1992. Crosstransplantation of kidneys in normal and Hyp mice. Evidence that the Hyp mouse phenotype is unrelated to an intrinsic renal defect. *The Journal of clinical investigation*, *89*(5), pp.1453-1459.

- *circulating factor that could be responsible in sets of experiments over nice. Miyauchi el al supported this by transplanting human tumor in nude mice which causes hypophosphatemia*[7].

I suggest to correct citation (7) and added to refereces

Miyauchi A, Fukase M, Tsutsumi M & Fujita T 1988 Hemangiopericytoma-induced osteomalacia: tumor transplantation in nude mice causes hypophosphatemia and tumor extracts inhibit renal 25-hydroxyvitamin D 1-hydroxylase activity. *Journal of Clinical Endocrinology and Metabolism* 67 46–53

Optional/General comments

This scientific paper is a case report.
The literature review focused on phosphaturic mesenchymal tumor are representative.
About 500 cases of TIO have been reported worldwide till in 2018.

Comment [i6]: Meyer RA Jr, Meyer M H & Gray RW 1989 Parabiosis suggests a humoral factor is involved in X-linked hypophosphatemia in mice. *Journal of Bone and Mineral Research* 4 493–500 doi:10.1002/jbmr.5650040407.
•Meyer RA, Jr, Meyer MH, Gray RW. Parabiosis suggests a humoral factor is involved in X-linked hypophosphatemia in mice. *J Bone Miner Res.* 1989 Aug;**4**(4):493–500. [PubMed] [Google Scholar]
•Meyer RA, Jr, Tenenhouse HS, Meyer MH, Klugerman AH. The renal phosphate transport defect in normal mice parabiosed to X-linked hypophosphatemic mice persists after parathyroidectomy. *J Bone Miner Res.* 1989 Aug;**4**(4):523–532. [PubMed] [Google Scholar]
Nesbitt, T., Coffman, T.M., Griffiths, R. and Drezner, M.K., 1992. Crosstransplantation of kidneys in normal and Hyp mice. Evidence that the Hyp mouse phenotype is unrelated to an intrinsic renal defect. *The Journal of clinical investigation*, *89*(5), pp.1453-1459.

Comment [i7]: Miyauchi A, Fukase M , Tsutsumi M & Fujita T 1988 Hemangio pericytoma-induced osteomalacia: tumor transplantation in nude mice causes hypophosphatemia and tumor extracts inhibit renal 25-hydroxyvitamin D 1-hydroxylase activity. *Journal of Clinical Endocrinology and Metabolism* 67 46–53 doi:10.1210/jcem-67-1-46.

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PART 2:

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Are there ethical issues in this manuscript?	*(If yes, Kindly please write down the ethical issues here in details)*	

Reviewer Details:

Name:	***Igna Cornel***
Department, University & Country	***University of Agricultural Science and Veterinary Medicine of Banat from Timisoara, Romania***