



Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

The first malignant primary hepatic glomus tumor: A case report

John G. Aversa^a, Cara Monroe^b, Amelia Levi^a, Antonios Papanicolau-Sengos^b, David E. Kleiner^b, Jonathan M. Hernandez^{a,*}^a Surgical Oncology Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA^b Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

ARTICLE INFO

Article history:

Received 9 March 2020

Accepted 19 April 2020

Available online 11 May 2020

Keywords:

Hepatic neoplasm

Malignant glomus tumor

Case report

Glomangiosarcoma

ABSTRACT

INTRODUCTION: Glomus tumors (GTs) are rare neoplasms that originate from the modified smooth muscle cells of glomus bodies and occasionally arise from visceral primary sites. All previously reported primary hepatic GTs were benign. Here we report the first malignant primary hepatic GT.

PRESENTATION OF CASE: Our patient is a 60-year-old male who presented with weight loss, early satiety, night sweats, and abdominal distention. Imaging demonstrated a large mass abutting the stomach, duodenum, and head of the pancreas, exerting mass effect on the portal vein and inferior vena cava. Biopsy results were deemed nondiagnostic after extensive review at multiple academic institutions. We performed a caudate lobe resection, antrectomy, and Bilroth II gastroduodenostomy that required skeletonization of much of the periportal vascular anatomy and the repair of multiple venotomies due to the tumor's adherence to the inferior vena cava. Histopathologic evaluation revealed morphologic and immunohistochemical findings consistent with a malignant GT, and next-generation sequencing using a targeted panel revealed an inactivating *TP53* mutation.

DISCUSSION: This case presented both a surgical and histopathologic challenge, requiring meticulous operative technique for resection in conjunction with a combination of characteristic morphologic features and immunohistochemical staining for diagnosis. Sequencing results using a targeted panel add to the limited GT genomic literature.

CONCLUSION: While rare, it is important to consider malignant GTs in the differential diagnosis for heterogeneous liver masses. Close follow-up will be essential to monitor our patient's clinical course and expeditiously pursue any further interventions.

Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Glomus tumors (GTs) are rare neoplasms derived from modified smooth-muscle cells of thermoregulatory glomus bodies. While GTs most frequently originate from within the dermis of the distal extremities, they can occasionally arise from visceral organs [1,2]. All seven previously reported primary hepatic GTs were benign [3–9]. Additionally, the molecular profile of malignant GTs has not been extensively characterized. Here we present the literature's first malignant primary hepatic GT and next-generation sequencing results from this rare tumor. This work has been reported in line with the SCARE criteria [10].

Abbreviations: GT, glomus tumor; PEComa, perivascular endothelial cell tumor; GIST, gastrointestinal stromal tumor; SMA, smooth muscle actin.

* Corresponding author at: 10 Center Drive, Building 10, Room 4-3740, Surgical Oncology Program, Center for Cancer Research, National Cancer Institute, Bethesda, MD 20814-3812, USA.

E-mail address: jonathan.hernandez@nih.gov (J.M. Hernandez).

2. Case presentation

2.1. Clinical course

A 60-year-old male with a history of ulcerative colitis presented with weight loss, early satiety, night sweats, and abdominal distention. Imaging revealed a large mass abutting the stomach, duodenum, and head of the pancreas exerting mass effect on the portal vein and inferior vena cava (Fig. 1A). Biopsy of the mass revealed a morphologically undifferentiated epithelioid and spindle cell tumor with indeterminate staining patterns. This sample was deemed nondiagnostic after histopathologic evaluation at multiple institutions. The patient was seen and denied an operation at multiple tertiary referral centers around the United States.

We evaluated the patient and offered him resection of the mass. Intraoperatively, we found that the tumor replaced the caudate lobe and was adhered to the gastric antrum. We performed a caudate lobe resection, antrectomy, and Bilroth II gastroduodenostomy. The operation required skeletonization of much of the periportal vas-

<https://doi.org/10.1016/j.ijscr.2020.04.067>

2210-2612/Published by Elsevier Ltd on behalf of IJS Publishing Group Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

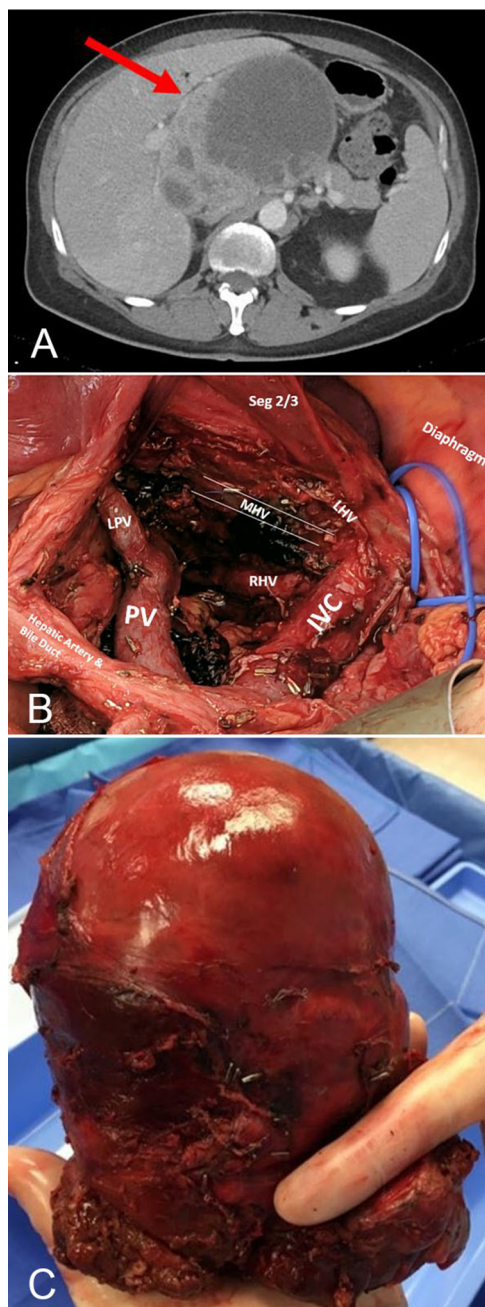


Fig. 1. (A) Axial aspect CT demonstrating a heterogenous lesion (red arrow) exerting mass effect on the surrounding vasculature as well as the stomach, duodenum, and head of the pancreas. (B) Intraoperative photograph of the skeletonized vasculature around the porta hepatis, demonstrating the extent of dissection required for surgical resection of this caudate lobe glomus tumor. As noted, the patient's diaphragm is oriented in the top right corner. Seg 2/3 = segments 2 and 3 of the liver, MHV = middle hepatic vein, LHV = left hepatic vein, RHV = right hepatic vein, IVC = inferior vena cava, PV = main portal vein, LPV = left portal vein. (C) Gross specimen with finger representing main portal vein's course prior to tumor removal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

cular anatomy and repair of multiple venotomies due to the tumor's adherence to the inferior vena cava (Fig. 1B). The patient tolerated the procedure well. Postoperatively he did experience a mild flare of his ulcerative colitis that resolved with medical therapy, but his course was otherwise unremarkable. He has demonstrated no evidence of recurrent disease and continues to follow up with our service.

Table 1
Detected genetic variants within the malignant glomus tumor.

Gene	Codon Mutation	Amino Acid Mutation	Variant Allele Frequency (%)
<i>TP53</i>	c.761 T>C	p.I254T	40
<i>TP53</i>	c.1134..1149del	p.R379fs	34
<i>ATRX</i>	c.6217+2T>A	N/A, splice site mutation	74
<i>ALOX12B</i>	c.284 G>A	p.R85H	27
<i>CREBBP</i>	c.2941 G>A	p.A981T	53
<i>SPTA1</i>	c.4823 G>A	p.R1608H	38

p.I254T = Isoleucine to threonine transition at amino acid 254.
p.R379fs = arginine frameshift mutation at amino acid 379.
p.R85H = Arginine to histidine transition at amino acid 85.
p.A981T = Alanine to threonine transition at amino acid 981.
p.R1608H = Arginine to histidine transition at amino acid 1608.

2.2. Pathology

Grossly, the resected specimen consisted of a large tan-brown mass measuring 18 cm in greatest dimension and weighing 890 g (Fig. 1C). There were solid and cystic components. The solid portion was dense, nodular, and tan-brown, with focal areas of necrosis. The cystic portion lacked an epithelial lining and contained bloody fluid with brown-gray coagulated material (Fig. 2A). Microscopic examination revealed plump, epithelioid round cells with eosinophilic, smooth cytoplasm and oval, hyperchromatic nuclei arranged in a trabecular pattern. The slits between the trabeculae were lined with thin endothelial cells (Fig. 2B–D). The mitotic count was 17 mitoses/50 high-powered fields, and atypical mitotic figures were identified (Fig. 2E). The tumor cells demonstrated smooth muscle actin (SMA) positivity by immunohistochemistry (Fig. 2F).

The tumor's site of origin and histomorphology prompted the consideration of a broad differential diagnosis that included primary hepatic sarcoma, angiosarcoma, leiomyosarcoma, hepatocellular carcinoma, cholangiocarcinoma, perivascular endothelial cell tumor (PEComa), hemangioendothelioma, primary hepatic neuroendocrine carcinoma, and gastrointestinal stromal tumor (GIST). While several diagnoses were less likely based on tumor morphology alone, immunohistochemical analyses further defined the neoplasm. Specifically, the tumor lacked the diffuse CD34 staining characteristic of angiosarcoma, the HMB-45 staining distinctive of PEComa, or the c-kit/CD117 staining typical of GIST. Although the tumor did demonstrate focal synaptophysin positivity, the absence of "salt and pepper" chromatin and a nest/chord arrangement ruled out the diagnosis of neuroendocrine tumor. Ultimately, the trabecular arrangement of distinctive, endothelial-lined epithelioid cells combined with positive SMA staining were typical of GT and secured the diagnosis. Furthermore, the tumor's extensive necrosis, atypical mitoses, elevated mitotic index, and vascular invasion were all suggestive of potential malignant behavior.

The GT's molecular profile was analyzed using a clinically-validated next-generation targeted sequencing assay (TruSight Oncology 500, Illumina, San Diego, CA), which detected six somatic mutations (Table 1). Among the detected variants, *TP53* I254T is a known inactivating mutation. The remaining variants are not well characterized, and their significance is unknown.

3. Discussion

Here we report the literature's first malignant primary hepatic GT and its molecular profile using a targeted panel of common cancer-causing mutations. While hepatic GT are exceedingly uncommon diagnoses, they should not be forgotten when evaluating heterogeneous liver lesions. GTs can originate from various visceral sites and can metastasize when malignant [1,2]. Metastatic GT can involve the liver, and the exclusion of a metastatic process

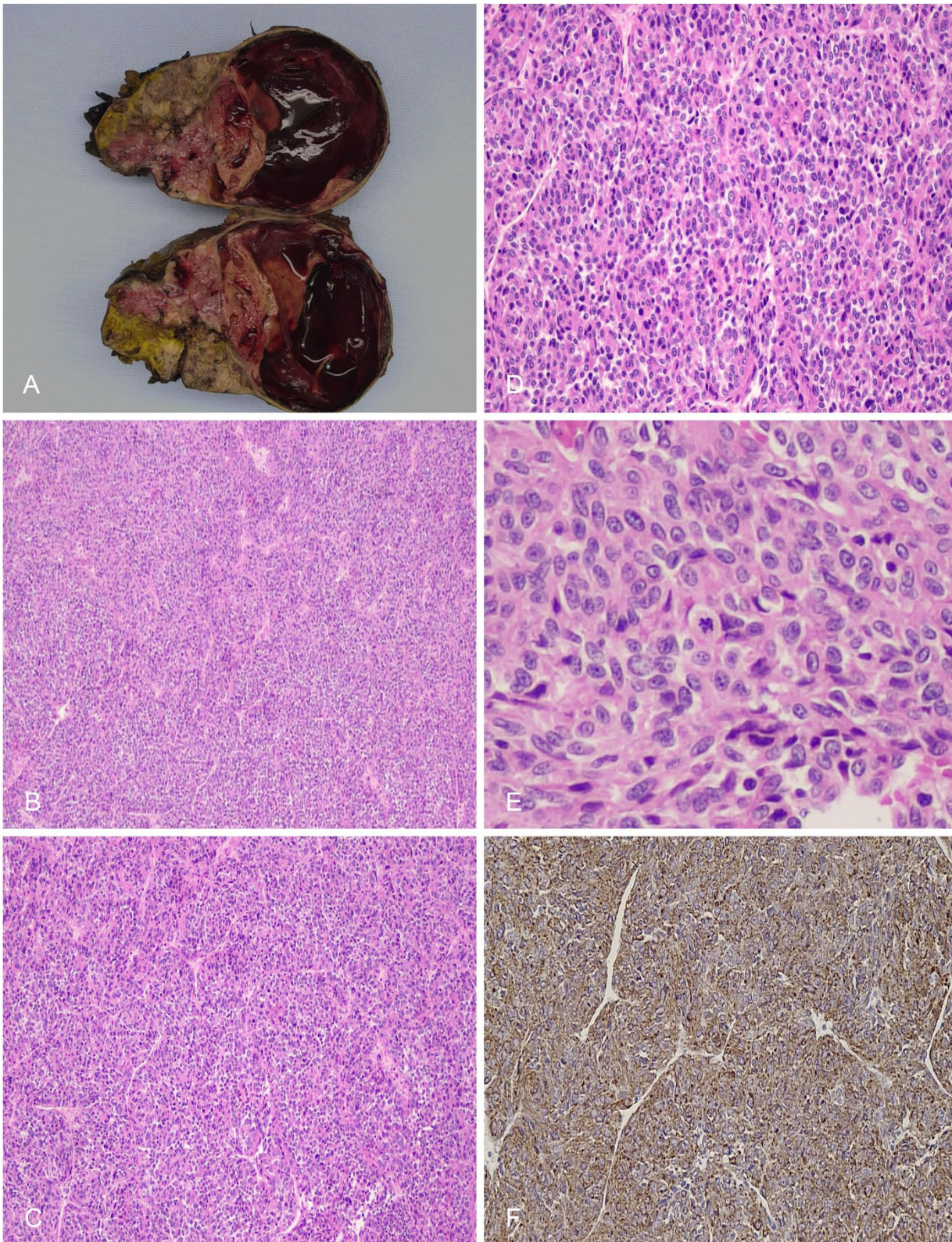


Fig. 2. Malignant Glomus Tumor of the Liver (Gross and Microscopic Photos) – (A) The liver mass was tan-brown measuring 18 cm in greatest dimension and composed of both a solid and a cystic area. (B) and (C) The tumor cells form a trabecular pattern demonstrated throughout the mass. (D) A higher magnification revealed plump, epithelioid round cells with eosinophilic, smooth cytoplasm and oval, hyperchromatic nuclei. Slits between the trabeculae are lined with thin, endothelial cells. (E) An atypical mitotic figure is surrounded by neoplastic cells displaying prominent nucleoli and atypia. (F) Tumor cells demonstrate the cytoplasmic staining with smooth muscle actin (SMA).

is crucial when managing any liver tumor. Our patient demonstrated no findings suggestive of additional pathology on physical exam, cross-sectional imaging, or metabolic imaging, which led us to conclude that his malignant GT was a primary hepatic process.

Survival implications due to the GT's malignant classification are unknown. Two prior GT series posited criteria for GT malignancy that included the presence of atypical mitotic figures and at least five mitoses per 50 high-powered fields [1,2]. Our patient's hepatic GT demonstrates both of these histomorphological criteria, in addition to clear vascular invasion, making it the only GT in the literature to do so. Additionally, while the GT's histopathologic findings suggest potential malignant behavior, the tumor's molecular profile provides little prognostic insight. Aside from an inactivating *TP53* mutation at amino acid 254, the GT demonstrated five variants that are poorly characterized, have not been described in malignant glomus tumors, and could represent either oncogenic mutations, passenger mutations, or private single nucleotide polymorphisms. Notably, our assay did not detect a *NOTCH2* translocation or *BRAF* V600E mutation, both of which are present in our panel assay and were reported in prior malignant GT genomic studies [11,12].

4. Conclusion

Overall, our case represents the first reported primary malignant hepatic GT and posed a diagnostic and surgical challenge. Close follow-up will be important to document the course of the patient's disease and plan any subsequent interventions in a timely fashion.

Conflicts of interest

The authors have no financial, personal, or organizational conflicts of interest.

Sources of funding

All funding support for this study was provided by the Intramural Research Program, National Cancer Institute, at the National Institutes of Health.

Ethical approval

Not applicable, the patient has given written informed consent for the publication of his case.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

Author contributions

John G. Aversa: Conceptualization, Methodology, Formal Analysis, Investigation, Writing-Original Draft, Writing- Review and Editing.

Cara Monroe: Methodology, Formal Analysis, Writing- Original Draft, Investigation, Formal Analysis, Visualization.

Amelia Levi: Conceptualization, Formal Analysis, Investigation, Writing- Review and Editing.

Antonios Papanicolau-Sengos: Methodology, Investigation, Validation, Formal Analysis, Writing- Review and Editing, Supervision.

David E. Kleiner: Methodology, Investigation, Validation, Formal Analysis, Writing- Review and Editing, Supervision.

Jonathan M. Hernandez: Conceptualization, Methodology, Formal Analysis, Investigation, Writing- Review and Editing, Supervision, Project Administration, Funding Acquisition.

Registration of research studies

NA.

Guarantor

Aversa JG, Hernandez JM.

References

- [1] A.L. Folpe, J.C. Fanburg-Smith, M. Miettinen, S.W. Weiss, Atypical and malignant glomus tumors: analysis of 52 cases, with a proposal for the reclassification of glomus tumors, *Am. J. Surg. Pathol.* 25 (1) (2001) 1–12, <http://dx.doi.org/10.1097/0000478-200101000-00001>.
- [2] M. Miettinen, E. Paal, J. Lasota, L.H. Sobin, Gastrointestinal glomus tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 32 cases, *Am. J. Surg. Pathol.* 26 (3) (2002) 301–311, <http://dx.doi.org/10.1097/0000478-200203000-00003>.
- [3] L. Li, Q.X. Xu, X.Y. Zhang, C.H. Han, Unusual location of the glomus tumour in the liver: a case report and literature review, *Medicine (Baltimore)* 97 (26) (2018), e11294, <http://dx.doi.org/10.1097/md.00000000000011294>.
- [4] H.J. Gassel, I. Klein, W. Timmermann, W. Kenn, A.M. Gassel, A. Thiede, Presentation of an unusual benign liver tumor: primary hepatic glomangioma, *Scand. J. Gastroenterol.* 37 (10) (2002) 1237–1240, <http://dx.doi.org/10.1080/003655202760373489>.
- [5] S. Amouelian, N.T. Meibodi, H. Tavooosi, V.R. Ekramifard, A. Attaranzadeh, M. Montazer, Primary glomus tumor of the liver, *Arch. Iran. Med.* 14 (4) (2011) 294–295, doi:0011144/aim.0015.
- [6] K. Hirose, T. Matsui, H. Nagano, H. Eguchi, S. Marubashi, H. Wada, et al., Atypical glomus tumor arising in the liver: a case report, *Diagn. Pathol.* 10 (2015) 112, <http://dx.doi.org/10.1186/s13000-015-0355-4>.
- [7] V.R. Jaiswal, J.G. Champine, S. Sharma, K.H. Molberg, Primary glomangioma of the liver: a case report and review of the literature, *Arch. Pathol. Lab. Med.* 128 (3) (2004) e46–9, [http://dx.doi.org/10.1043/1543-2165\(2004\)128<e46:PGOTLA>2.0.CO;2](http://dx.doi.org/10.1043/1543-2165(2004)128<e46:PGOTLA>2.0.CO;2).
- [8] B. Geramizadeh, S. Nikeghbalian, A. Shamsaifar, K. Kazemi, H. Tavooosi, S. Sefidbakht, et al., Primary glomus tumor of the liver: a rare case report and review of the literature, *Indian J. Pathol. Microbiol.* 54 (3) (2011) 584–587, <http://dx.doi.org/10.4103/0377-4929.85101>.
- [9] A. Kihara, J. Fukushima, H. Horiuchi, Glomus tumor of the liver presenting as a cystic lesion, *Pathol. Int.* 64 (6) (2014) 295–297, <http://dx.doi.org/10.1111/pin.12169>.
- [10] R.A. Agha, M.R. Borrelli, R. Farwana, K. Koshy, A.J. Fowler, D.P. Orgill, et al., The SCARE 2018 statement: updating consensus surgical CAse REport (SCARE) guidelines, *Int. J. Surg.* 60 (2018) 132–136, <http://dx.doi.org/10.1016/j.ijsu.2018.10.028>.
- [11] N. Karamzadeh Dashti, A. Bahrami, S.J. Lee, S.M. Jenkins, F.J. Rodriguez, A.L. Folpe, et al., BRAF V600E mutations occur in a subset of glomus tumors, and are associated with malignant histologic characteristics, *Am. J. Surg. Pathol.* 41 (11) (2017) 1532–1541, <http://dx.doi.org/10.1097/pas.0000000000000913>.
- [12] J.M. Mosquera, A. Sboner, L. Zhang, C.L. Chen, Y.S. Sung, H.W. Chen, et al., Novel MIR143-NOTCH fusions in benign and malignant glomus tumors, *Genes Chromosomes Cancer* 52 (11) (2013) 1075–1087, <http://dx.doi.org/10.1002/gcc.22102>.

Open Access

This article is published Open Access at [sciencedirect.com](https://www.sciencedirect.com). It is distributed under the [IJSCR Supplemental terms and conditions](#), which permits unrestricted non commercial use, distribution, and reproduction in any medium, provided the original authors and source are credited.