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Author's response to reviewers' and editors' comments

Dear editor and reviewers:

Thank you for your letter and for the comments concerning our manuscript, entitled "MRI features of intrahepatic extramedullary hematopoiesis from three case reports" (Manuscript NO.: 74029, Case Report). Those comments are all constructive for improving our paper. We have studied comments carefully and have made correction which we hope meet with approval.

The responses point-by-point are as follow:

Reviewer's comments

Reviewer #1:

Specific Comments to Authors: These are interesting cases. However, I would like the authors to describe in detail the differential diagnosis: what MRI data are characteristic of extramedullary hematopoiesis, for which disorders these changes are also characteristic, and how, ultimately, to distinguish extramedullary hematopoiesis from these disorders. You should also spell out all the abbreviations.

Response:

We thank for the reviewer's suggestion. We have added the differential diagnosis in the Discussion section according to your advice:

"……More reports are warranted to be documented in the future.

The differential diagnosis includes benign, primary, and secondary liver malignant lesions. IEMH may mimic these lesions leading to troublesome diagnosis. In the "fat deposition" stage, the characteristic signal intensity on the in-phase image is higher than that on the out-phase image. The differential diagnosis in cirrhotic liver includes fatty metamorphosis in HCC, while that in non-cirrhotic liver includes benign lesions such as focal fatty infiltration (without mass effect), adenoma (hepatocyte nuclear factor 1a–mutated subtype) and lipoma (no enhancement). Angiomyolipoma should be also taken into consideration. In the "iron deposition" stage, the characteristic signal intensity on the in-phase image is lower than that on the out-phase image. The differential diagnosis (intratumoral bleeding) includes benign lesions such as adenoma (inflammatory subtype) and hemangioma. Malignant lesions include hemorrhagic HCC and metastasis. When IEMH demonstrates strong and persistent enhancement, FNH, adenoma and hypervascular metastasis need to be considered. An appropriate clinical setting and the application of Gd-EOB-DTPA or superparamagnetic iron oxide are helpful for diagnosis. When IEMH shows mild enhancement or avid enhancement with "washout", atypical metastasis, HCC, or even fibrolamellar carcinoma in young patients should be considered in the differential list. Lymphoma is homogenous isointense with moderate enhancement. Fat and bleeding content is seldom seen in lymphoma."

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Reviewer #2:

Specific Comments to Authors: In this manuscript, the authors reported 3 cases with intrahepatic extramedullary hematopoiesis and aim to provide more radiologic appearance of MRI and help radiologists establish diagnostic consideration. In general, the data descriptions of the three patients are detailed and the discussions are appropriate. However, these comments are aimed at further improving the quality of the manuscript. 1. First, in the discussion part, a summary of the reported imaging features of IEMH from published papers in the form of tables, especially MRI features, can make the content clearer and more intuitive.

Response:

We thank for the reviewer's advice. We have added Table 1 in the text.

"……There have been discrepancies on the radiologic characteristics of different studies (Table 1). IEMH was described as fat-containing lesion……"

Table 1. Clinical and MRI features of 9 cases with intrahepatic extramedullary hematopoiesis

Case	*T1WI (compare to liver)*	*T2WI (compare to liver)*	*In/out-phase*	*Enhancement*	*Underlying condition*
Case 1	*Hypointense*	*Heterogenous*	*In-phase lower, out-phase high*	*Heterogenous and persistent*	*Thyroid carcinoma and lung adenocarcinoma*
Case 2	*Slightly hypointense*	*Slightly hyperintense*	*In-phase lower, out-phase high*	*Delayed*	*Hodgkin's lymphoma*
Case 3	*Hypointense*	*Hyperintense*	*In-phase lower, out-phase high*	*Avid in arterial phase and "washout" in later phases*	*Unknown*
Lee[2]	*Slightly hypointense*	*Hyperintense*	*N/A*	*Homogeneous, avid and persistent*	*Idiopathic myelofibrosis*
Belay[8]	*Hypointense*	*Hypointense[1]*	*N/A*	*Avid and persistent*	*Myelodysplastic syndrome*
Zhang[9]	*Slightly hypointense*	*Hyperintense*	*Without signal intensity change*	*Homogeneous avid in arterial phase and isointense in later phases*	*Idiopathic myelofibrosis*
Tamm[12]	*Hypointense*	*Hyperintense*	*N/A*	*Delayed*	*Gaucher disease*
Jelali[23]	*Slightly hyperintense*	*Slightly hyperintense*	*N/A*	*Delayed*	*Sickle cell disease*
Wong[24]	*Hyperintense*	*Heterogenous*	*N/A*	*Delayed*	*β-Thalassaemia*

*MRI: magnetic resonance imaging; WI: Weighted image; N/A: not performed or evaluated; [1]: evaluated by the T2*WI.*

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2. Since most of these patients had hematological diseases. According to the author's description, the first patient and the third patient have no evidence of hematological diseases. Please add the discussion about this.

Response:

We appreciate the reviewer's advice. We have added discussion to the text according to your advice:

"……and the lack of exclusive imaging patterns.

Although most of the patients with IEMH had hematological disease, a few cases had no evidence of this underlying condition (as shown in the Case 1 and Case 3). For example, patients with small cell lung cancer and Noonan syndrome were reported in two cases[4, 15], and the cause of IEMH in another two cases remains unknown[21, 22]."

*[4] **Bradley MJ**, Metreweli C. Ultrasound appearances of extramedullary haematopoiesis in the liver and spleen. Br J Radiol 1990; **63**: 816-818 [PMID: 2242486 DOI: 10.1259/0007-1285-63-754-816]*

*[15] **Gupta P**, Naran A, Auh YH, Chung JS. Focal intrahepatic extramedullary hematopoiesis presenting as fatty lesions. AJR Am J Roentgenol 2004; **182**: 1031-1032 [PMID: 15039182 DOI: 10.2214/ajr.182.4.1821031]*

*[21] **Warshauer DM**, Schiebler ML. Intrahepatic extramedullary hematopoiesis: MR, CT, and sonographic appearance. J Comput Assist Tomogr 1991; **15**: 683-685 [PMID: 2061490]*

*[22] **Du E**, Overstreet K, Zhou W, Baird G, Baird S, Bouvet M, Haghighi P. Fine needle aspiration of splenic extramedullary hematopoiesis presenting as a solitary mass. A case report. Acta Cytol 2002; **46**: 1138-1142 [PMID: 12462096 DOI: 10.1159/000327121]*

3. Please add the arrows indicating the lesions into Figure1 and Figure 3.

Response:

We appreciate the reviewer's suggestion. We have added the arrows into Figure 1 and Figure 3.

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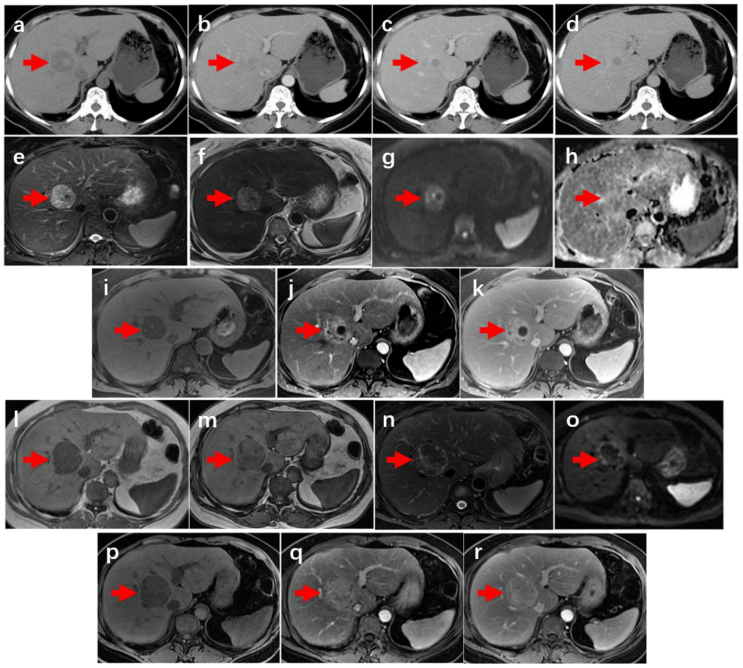

Figure 1 An intrahepatic mass (arrow) in Segment VIII was found in a 50-year-old female. (a) On unenhanced CT, the lesion was heterogeneously hypodense, with hyperdense foci in the central area. The lesion became heterogeneously hyperdense in the arterial phase (b), progressive enhancement in the portal venous (c) and delayed phase (d). (e-k) On magnetic resonance imaging, the lesion showed heterogeneously hyperintense on T2WI (weighted image), T2WI-FS (fat saturation) (e, f) and DWI (diffusion weighted imaging) (g), isointense on apparent diffusion coefficient map (h), hypointense on T1WI-FS (i), avid enhancement on arterial phase (j) and persistent enhancement on delayed phase (k). (l-r) Corresponding follow-up images five months later showed the lesion size increasement. Signal drop was seen on in-phase (l) compared with out-phase (m). The lesion demonstrated heterogeneously hypointense on T2WI-FS (n) and DWI (o), homogeneous hypointensity on T1WI-FS (p), hypervascular enhancement with delayed enhancement on arterial (q) and delayed phase (r), respectively. The surgical pathologic confirmation was intrahepatic extramedullary hematopoiesis.

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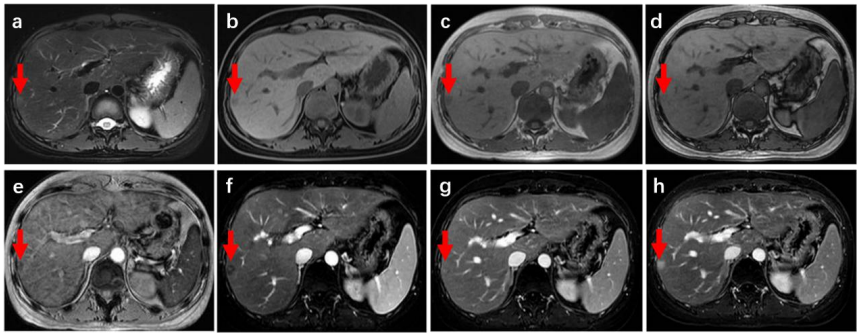

Figure 3 A 30-year-old female diagnosed with intrahepatic extramedullary hematopoiesis was confirmed by biopsy. The lesion (arrow) located in the subcapsular of Segment VI/VII showed slightly hyperintense on T2WI-FS (a) and slightly hypointense on T1WI-FS (b). The lesion was lower signal intensity on in-phase (c) than that on out-phase (d), and signal loss on susceptibility weighted imaging (e). In dynamic series, the lesion was mild enhancement in the arterial phase (f), with areas of progressive and prolonged enhancement in the portal venous (g) and delayed phases (h).

Reviewer #3:

Specific Comments to Authors: Authors report radiologic appearances of IEMH which are easily misdiagnosed. Given its rarity and the lack of pathognomonic imaging findings, awareness of these presentations will help clinicians in diagnosis.

Response:

We thank for the reviewer's comments. We hope more imaging findings of IEMH could be shared, helping radiologists and clinicians in diagnosis.

Reviewer #4:

Specific Comments to Authors: Thank you for your submission. Your manuscript was an interesting read. But the manuscript is not well organized and does not follow a clear flow. Please see the following comments about how your data could be further clarified:

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• This manuscript has no introduction. There is a paragraph at the beginning of the manuscript but they have no reference. It is not clear whether this is an introduction or not.

Response:

We appreciate that the reviewer pointed this out. We have added reference citation to the "Introduction" section.

INTRODUCTION

Extramedullary hematopoiesis seldom occurs within the liver alone[1]. In this rare condition, the lesion can manifest as a mass with no typical radiologic findings, making it difficult to diagnose and differentiate from other hypervascular neoplasms[2]. We here present three cases of intrahepatic extramedullary hematopoiesis (IEMH) occurring solely in the liver. These lesions showed lower signal intensity on in-phase image than those on out-phase image. In addition, the first case is unique in that the lesion showed changes in magnetic resonance imaging (MRI) signal intensity with size enlargement between two rounds of imaging examination. These manifestations have never been reported before.

*[1] **Roberts AS**, Shetty AS, Mellnick VM, Pickhardt PJ, Bhalla S, Menias CO. Extramedullary haematopoiesis: radiological imaging features. Clin Radiol 2016; **71**: 807-814 [PMID: 27377325 DOI: 10.1016/j.crad.2016.05.014]*

*[2] **Lee IJ**, Kim SH, Kim DS, Lee JM, Han JK, Choi BI. Intrahepatic extramedullary hematopoiesis mimicking a hypervascular hepatic neoplasm on dynamic- and SPIO-enhanced MRI. Korean J Radiol 2008; **9 Suppl**: S34-S38 [PMID: 18607123 DOI: 10.3348/kjr.2008.9.s.s34]*

• The author describes three cases but there is no order in the description. Some explanations are very much and some are very brief.

Response:

We appreciate the reviewer's warning. We have rewritten and rearranged the manuscript structure (CASE PRESENTATION, FINAL DIAGNOSIS, TREATMENT and OUTCOME AND FOLLOW-UP sections) according to the Guidelines and Requirements for Manuscript Revision and the Format for Manuscript Revision: Case Report.

• Writing case articles has a rule of thumb that makes it easy for readers to read and compare cases, which you will not see in this handwriting.

Response:

We thank for the reviewer's comment. We have rewritten and rearranged the manuscript structure (CASE PRESENTATION, FINAL DIAGNOSIS, TREATMENT and OUTCOME AND FOLLOW-UP sections) according to the Guidelines and Requirements for Manuscript Revision and the Format for Manuscript Revision: Case Report.

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• There are 18 images for Figure 1, 4 images for Figure 2, 8 images for Figure 3, 8 images for Figure 4, and 5 images for Figure 5, which are very difficult and confusing to understand that putting all these images in this shape is not understandable.

Response:

We thank for the reviewer's advice. We have rearranged these figures according to your advice. There are 5 figures in the manuscript. Please see below.

• There is no description for images (a, b, c, d, e ...) in the manuscript.

Response:

We appreciate that the reviewer pointed this out. We have added description for each figure in the manuscript.

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Figure Legends

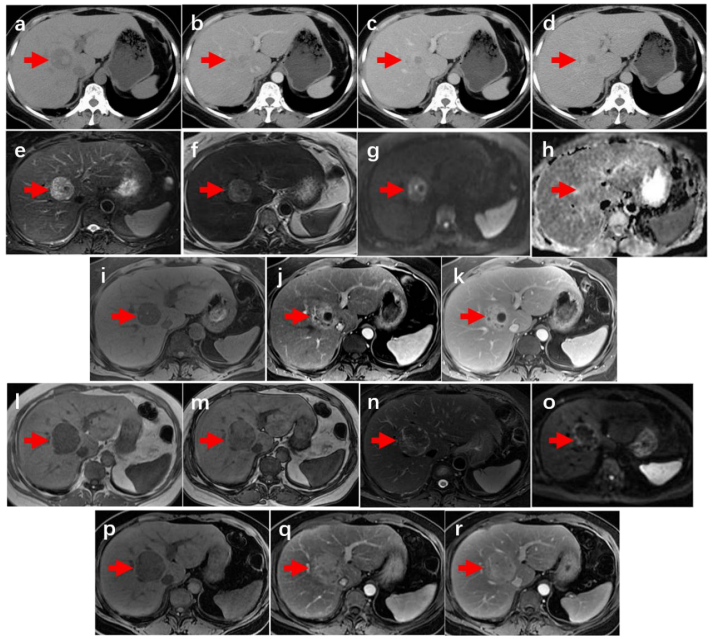

Figure 1 An intrahepatic mass (arrow) in Segment VIII was found in a 50-year-old female. (a) On unenhanced CT, the lesion was heterogeneously hypodense, with hyperdense foci in the central area. The lesion became heterogeneously hyperdense in the arterial phase (b), progressive enhancement in the portal venous (c) and delayed phase (d). (e-k) On magnetic resonance imaging, the lesion showed heterogeneously hyperintense on T2WI (weighted image), T2WI-FS (fat saturation) (e, f) and DWI (diffusion weighted imaging) (g), isointense on apparent diffusion coefficient map (h), hypointense on T1WI-FS (i), avid enhancement on arterial phase (j) and persistent enhancement on delayed phase (k). (l-r) Corresponding follow-up images five months later showed the lesion size increasement. Signal drop was seen on in-phase (l) compared with out-phase (m). The lesion demonstrated heterogeneously hypointense on T2WI-FS (n) and DWI (o), homogeneous hypointensity on T1WI-FS (p), hypervascular enhancement with delayed enhancement on arterial (q) and delayed phase (r), respectively. The surgical pathologic confirmation was intrahepatic extramedullary hematopoiesis.

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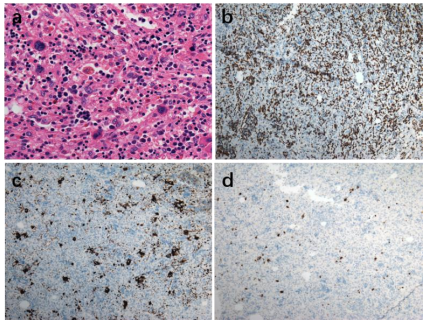

Figure 2 Intrahepatic extramedullary hematopoiesis in the same patient of Figure 1. (a) On the photomicrograph (Hematoxylin & Eosin staining; ×200), megakaryocytes and erythroid cells were scattered within surgical specimen. (b-d) Immunohistochemical staining using CD235 (b), CD61 (c) and MPO (d) marker (×40) revealed that cells were positive (brown color), respectively.

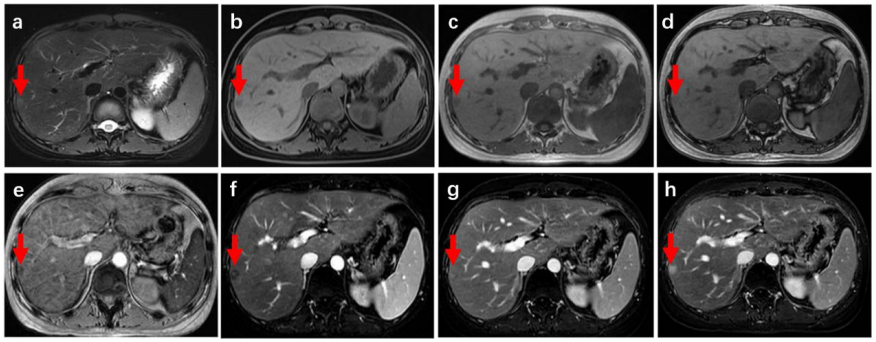

Figure 3 A 30-year-old female diagnosed with intrahepatic extramedullary hematopoiesis was confirmed by biopsy. The lesion (arrow) located in the subcapsular of Segment VI/VII showed slightly hyperintense on T2WI-FS (a) and slightly hypointense on T1WI-FS (b). The lesion was lower signal intensity on in-phase (c) than that on out-phase (d), and signal loss on susceptibility weighted imaging (e). In dynamic series, the lesion was mild enhancement in the arterial phase (f), with areas of progressive and prolonged enhancement in the portal venous (g) and delayed phases (h).

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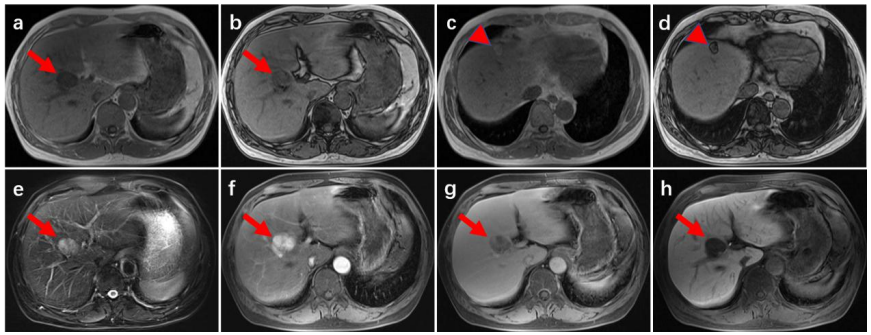

Figure 4 A 52-year-old male diagnosed with intrahepatic extramedullary hematopoiesis was confirmed by resection. The lesion located in the Segment V/VIII (arrow) showed lower signal intensity on in-phase (a) than that on out-phase (b), opposed to another lesion (the same patient) in the Segment IV (arrowhead, the surgical pathologic confirmation was angioleiomyolipoma), which was higher signal intensity on in-phase (c) than that on out-phase (d). The lesion (arrow) was high signal intensity on T2WI-FS (e), with intense enhancement in the arterial phase (f), relative hypointense in the transitional phase (g) and hepatobiliary phase (h).

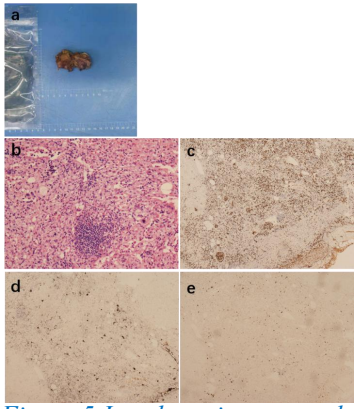

Figure 5 Intrahepatic extramedullary hematopoiesis in the same patient of Figure 4. (a) Photograph of the specimen showed lobular and solid nature of the resected hepatic mass (Segment V/VIII), without areas of necrosis and hemorrhage. (b) On the photomicrograph (Hematoxylin & Eosin staining; ×200), granulocytes, megakaryocytes, adipocyte and erythrocyte were distributed within surgical specimen. (c-e) Immunohistochemical staining using CD235 (c), CD61 (d) and MPO (e) marker (×40) revealed that cells were positive (brown color), respectively.

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EDITORIAL OFFICE'S COMMENTS

(1) Science editor:

5. Issues raised:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

Response:

We thank for the science editor's inspection. We have added the "Author Contributions" in the system.

Author Contributions: Luo M and Chen JW collected the data; Luo M, Chen JW and Xie CM analyzed the data; Luo M wrote the original draft; Xie CM reviewed and edited the manuscript; all authors have read and approve the final manuscript.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response:

We appreciate that the science editor pointed it out. We have prepared the figures in the PowerPoint which submitted as "74029-Figures.ppt" on the system.

(3) The "Case Presentation" section was not written according to the Guidelines for Manuscript Preparation. Please re-write the "Case Presentation" section, and add the "FINAL DIAGNOSIS", "TREATMENT", and "OUTCOME AND FOLLOW-UP" sections to the main text, according to the Guidelines and Requirements for Manuscript Revision.

Response:

We thank the science editor for the suggestion. We have rewritten the "CASE PRESENTATION" section and added the "FINAL DIAGNOSIS", "TREATMENT" and "OUTCOME AND FOLLOW-UP" sections to the main text according to the Guidelines and Requirements for Manuscript Revision and the Format for Manuscript Revision: Case Report.

(2) Company editor-in-chief:

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Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Response:

We appreciate the warning from the company editor-in-chief. We have prepared the decomposable figures in the PPT and submitted as "74029-Figures.ppt" on the system.

Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

Response:

We appreciate the warning from the company editor-in-chief. We have rechecked, and we confirm that all of these figures are original. We have added the copyright information "Copyright ©The Author(s) 2022" to the bottom right-hand side of each picture in the "74029-Figures.ppt" according to your request.