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Radiologic and Histopathologic Correlation of Different Growth Patterns of Metastatic Uveal Melanoma to the Liver:

MRI/Pathology of Metastatic UM

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Abstract

Purpose: The purpose of this study was to correlate magnetic resonance imaging (MRI) radiographic results with histopathologic growth patterns of metastatic uveal melanoma (UM) to the liver.

Design: Clinicopathologic correlation.

Subjects: Patients with metastatic UM to the liver.

Methods—A retrospective review of MRI images of patients with metastatic UM to the liver at a single institution between 2004–2016 was performed. The MRI growth patterns were classified as nodular or diffuse. The histopathologic findings in core liver biopsies of liver metastases identified by needle localization in a subset of these patients were reviewed. The core samples were evaluated by routine light microscopy including immunohistochemical/immunofluorescent staining for CD31, CD105 and HMB45 and classified as exhibiting an infiltrative or nodular growth pattern.

Outcome measures: MRI images and core biopsy findings.

Results—Thirty-two patients were identified with metastatic UM to the liver that was imaged by MRI and 127 lesions were identified. There were 46 lesions that were classified by MRI as infiltrative and 81 as nodular. There were 9 needle-localized core biopsies that corresponded to MRI-imaged metastatic lesions. Of these 9 lesions, 3 that were classified as infiltrative on MRI exhibited a stage I infiltrative histologic growth patterns; of the remaining 6 that were classified as

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nodular by MRI, 5 histologically demonstrated stage II or stage III infiltrative growth patterns and 1 histologically demonstrated a nodular growth pattern.

Conclusions—MRI hepatic infiltrative growth patterns of metastatic UM corresponded to stage I histologic infiltrative growth in the sinusoidal spaces whereas MRI nodular growth patterns corresponded to either stage II/ III histologic infiltrative growth that replaced the hepatic lobule or histologic nodular growth in the portal triad that effaced adjacent hepatic parenchyma.

Introduction

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults.¹ UM accounts for 3.7% of all reported melanoma cases in the United States² and its mean age-adjusted incidence is approximately 5.1 per million.³ Current treatment methods for UM include transpupillary thermotherapy, brachytherapy, proton beam irradiation, local resection, and enucleation.^{4,5} Despite the development of effective local therapies, the 5-year survival rate for patients with UM has not changed over the past three decades, remaining at approximately 80%. This can partially be attributed to the high rate of metastasis in these patients (~50%) coupled with the fact that there is no effective adjuvant therapy.^{6,7} The one-year survival rate for patients with metastatic UM is approximately 15%, with reported median survivals ranging from 4 to 15 months.⁸

The liver is the most common site of metastasis for UM; it is the initially detected metastatic site in greater than 60% of patients.⁹ Hepatic metastases are present in greater than 90% of patients with metastatic disease.¹⁰ It is important to understand the growth characteristics of UM in the liver with regard to diagnosis and therapy. Our laboratory has characterized the existence of two distinct histologic growth patterns of metastatic UM in the liver.¹¹ The ‘lobular’ or ‘infiltrative’ pattern refers to tumor infiltration directly into the hepatic lobules that is accompanied by perilobular septal fibrosis. The ‘portal’ or ‘nodular’ pattern describes distinct clusters of tumor cells located around the portal venules in the portal triad that push aside, or “efface”, the neighboring liver parenchyma. In the infiltrative pattern, tumor cells receive their nutrition from blood in the sinusoidal or pseudosinusoidal spaces and there is minimal angiogenesis.¹² In the nodular pattern, the tumor co-opts adjacent portal venules, exhibits angiogenesis as the metastatic focus enlarges, and new tumor blood vessels extend from branches of the hepatic arteriole.^{11,12}

Several radiographic studies have also identified differential growth patterns of metastatic UM in the liver; importantly, identification of these growth patterns have clinical implications. For example, tumors with a radiographic nodular growth pattern on angiography appear to be more responsive to chemoembolization or radioembolization compared to tumors classified with a radiographic infiltrative pattern.^{13–15} Until now, the relationship between these radiographic and histopathologic growth patterns has not been explored. In this study, we evaluated the MRI features of metastatic UM to the liver and correlated findings with histopathologic patterns from biopsies.

Materials and Methods

We retrospectively evaluated all patients diagnosed with hepatic metastases from malignant melanoma of the choroid who had sequential imaging done at Emory University from January 1st, 2004 to September 1st, 2016. This study was approved by the Emory University School of Medicine Institutional Review Board, Atlanta, GA. Our protocol for imaging is described in the Table 1 (see online resource). Visceral metastases from melanoma have a wide variety of appearances on MR images. The pattern of tumor vascularity is exploited for detection of liver metastases in gadolinium chelate-enhanced MR imaging.¹⁶ Hyper-vascular liver metastases are usually from primary tumors such as melanoma, neuroendocrine tumors including carcinoid, islet cell tumors, renal cell carcinoma, and thyroid carcinoma. These hypervascular metastases show peak enhancement in hepatic arterial phase and were obtained at 20 seconds post contrast injection as fat suppressed T1-weighted images. The imaging appearance of liver metastases on portal venous and delayed phases can be variable and images were acquired at 70 seconds and 180 seconds post contrast injection, respectively, as fat suppressed T1-weighted images. As UM metastatic lesion scans show high T1 signal on non-contrast images due to the presence of melanin (Figure 1), it can be challenging to determine enhancement following contrast, therefore subtraction images were used.¹⁷ Liver metastases from melanoma may also show transient peripheral rim enhancement in the arterial phase (Figure 2).¹⁸ Our institution preferentially uses MR for liver imaging due to superior soft tissue contrast and lack of ionizing radiation as these patients require frequent follow-ups to assess treatment response.

An experienced radiologist (PM) assessed the radiographic images. Patients' core biopsy samples, if available, were matched with the radiographic biopsy site. This was performed by reviewing patient biopsy reports and visualizing the core needle entering the lesion in question on MRI and CT imaging. For each of these cases, sections of the core liver biopsies with suspected metastasis were obtained and reviewed by an experienced pathologist (HEG). Patient samples were pseudoanonymized for data other than age and sex. All biopsy samples were routinely processed and stained with hematoxylin and eosin (H&E), Masson trichrome and reticulin. Immunohistochemical (IHC) staining using CD31 (DAKO, Carpinteria, CA 1:180) was used to evaluate for the presence of vascular channels (CD31+) and immunofluorescence (IF) staining for CD105 (DAKO, 1:5) was used to identify new vascular endothelium (CD105+). IHC stains for HMB45 (DAKO, 1:50) were used to confirm the melanoma. CD31 stains mature vascular endothelium.¹⁹ CD105 is a transforming growth factor beta (TGF- β) receptor expressed in embryonic endothelial cells; its presence indicates angiogenesis.²⁰ The H&E, Masson trichrome, and IHC-stained slides were examined by light microscopy to determine presence and histologic growth pattern of the metastases (nodular or infiltrative) as previously described.^{11,12} The radiographic features were evaluated in a masked fashion and then compared with the corresponding histologic growth patterns.

Results

We identified 32 patients who were diagnosed with metastatic UM and had hepatic imaging. The average age of the patients was 58.5 years and there were 21 male and 11 female

patients. The treatments for the primary tumors in these patients were brachytherapy with an iodine-125 plaque in 16 patients, enucleation for 13 patients, external beam radiation for 1 patient, subsequent enucleation after plaque failure for 1 patient, and plaque therapy with laser photocoagulation in 1 patient. The treatment of metastatic disease was the following: chemotherapy or chemoimmunotherapy was administered to 14 patients; 1 patient received radioablation; 1 patient had a resection as the sole treatment; 8 patients had a combination of chemotherapy/chemoimmunotherapy/embolization; 1 patient had laser ablation/chemoimmunotherapy; 1 patient had radiation/chemoimmunotherapy; 2 patients had only embolization; 1 patient had no treatment; 3 patients did not have treatment records available.

A total of 127 lesions were followed radiographically from this patient population. Classically, UM metastases may reveal a hyperintense signal on unenhanced T1 weighted MR images due to the paramagnetic effect of melanin, which is present in minority of cases. . More commonly, lesions were either hypointense or isointense on T1-weighted sequences and hyperintense on T2-weighted sequences. Two predominant patterns were seen on MRI imaging. The MRI infiltrative pattern as shown in Figure 3 was characterized as an enlarged, extensive heterogeneous enhancement of the liver that does not respect the liver lobule boundaries and had no distinct nodularity. The MRI nodular pattern, as shown in Figure 4, consisted of multiple, hyperenhancing lesions in the liver with defined boundaries that were distinct from the surrounding parenchyma. In total, there were 46 lesions that were classified as infiltrative on imaging, and 81 lesions that were classified as nodular on imaging. Twelve patients had both infiltrative and nodular lesions on imaging.

We had access to core biopsy pathology samples for nine patients. Three of these nine patients were biopsied from lesions that demonstrated the MRI infiltrative pattern; their biopsies showed the stage I infiltrative pattern characterized by micrometastatic collections of melanoma cells (1–51 μ m in diameter) within reticulin-lined sinusoidal spaces (Figure 5). IHC/IF staining confirmed the melanoma with HMB45 positivity and showed that these infiltrates contained CD31+ /CD105– endothelial cells, consistent with the endothelial lining of the sinusoidal spaces. Extensive MRI infiltrative lesions that occupied a substantial portion of the liver radiographically were also comprised of these histologic stage I infiltrative micrometastases.

The remaining six patients had lesion biopsies that were classified by MRI to be nodular. There were two distinct histologic patterns in these MRI nodular lesions. Five biopsies exhibiting MRI “nodular” patterns corresponded to a histopathologic infiltrative pattern. These tumors were either stage II infiltrative (Figure 6), which were composed of expanded metastases (51 – 500 μ m in diameter) in the sinusoidal spaces containing stellate cell lined pseudosinusoidal spaces and collagen bands that were remnants of the lobular architecture, or stage III infiltrative metastases (greater than 500 μ m in diameter, Figure 7), which replaced the hepatic lobule and contained only thin strands of collagen remnants of the original hepatic lobule.¹¹ The collagen remnants were highlighted by the trichrome stain. Much like the stage I infiltrative pattern, these lesions contained CD31+/CD105– sinusoidal endothelium. We classified these lesions as “pseudonodules” which formed from the histologic infiltrative growth pattern. One of these histologic patterns was composed of a tumor nodule that lacked any lobular or residual lobular architecture, including a lack of

collagen strands, and contained CD31+/CD105+ endothelium from neovascularization (Figure 8). Of note, the tissue core in biopsies of the infiltrative pattern held together due to the collagen scaffold from the hepatic lobule whereas the tissue core from the biopsy of the nodular pattern fell apart as there was no collagen scaffold from the hepatic lobule. In short, our results showed that the *MRI infiltrative* pattern corresponded to the *histologic stage I infiltrative* pattern, whereas the *MRI nodular* pattern corresponded to either the *histologic stage II/stage III infiltrative* patterns (pseudonodules) or *histologic nodular* pattern.

Discussion

There have been few studies examining the radiographic features of metastatic UM in the liver and none that compared the radiographic and pathologic findings although MRI is the recommended imaging modality for uveal melanoma liver metastases.^{14,21–23} We had previously characterized the progression of metastatic UM in the liver histopathologically.^{11,12} Our studies have demonstrated the presence of two distinct histologic growth patterns. In the histologic infiltrative pattern, UM invades into the sinusoidal spaces of the hepatic lobule and eventually replaces the hepatocytes in the lobule with associated intralobular collagen remnants and perilobular fibrosis. In this growth pattern, islands of tumor cells (micrometastases) receive nutrition from blood in the sinusoidal spaces. As the size (diameter) of islands of tumor grows from stage I (<50µm) to stage II (50–500 µm) and stage III (>500 µm), pseudosinusoidal spaces lined by stellate cells form, thus allowing the tumor to be bathed with blood and obviate angiogenesis. As the tumor replaces the hepatic lobule and is surrounded by thickened fibrous septae, the original collagen strands from the lobule remain, and there may be minimal angiogenesis in the areas of the septae surrounding the lobule in stage III.

In the histopathologic nodular growth pattern, clusters of tumor cells initially form within the portal triad, co-opt the hepatic venule for nutrition, and eventually enlarge into a nodule that pushes aside (effaces rather than invades) the adjacent liver parenchyma. There is no lobular or residual lobular architecture; this includes a lack of collagen; at this point, tumor neovascularization occurs to supply nutrition to the nodule. The neovascularization (angiogenesis) extends from the hepatic arteriole, which is present in the portal triad.

Our study sought to determine whether the histologic definition of nodular versus infiltrative growth corresponded to MRI imaging of hepatic metastases of UM. On imaging, two distinct MRI patterns of UM were recognized. The MRI nodular pattern was characterized by discrete, well-defined tumor foci, while the MRI infiltrative pattern was diffuse and lacked distinct borders. Although we found that the MRI infiltrative pattern corresponded to the histologic stage I infiltrative pattern, we recognized that the MRI nodular pattern corresponded to either the histologic stage II or III infiltrative or nodular growth patterns. Specifically, stage II and stage III histologic infiltrative UM metastasis can grow and eventually replace the entire hepatic lobule, becoming surrounded by thickened collagenous septae. This results in a focal, distinct nodule on MRI imaging (Figure 9). We classified this later growth pattern as a pseudonodule, a characterization that can only be elucidated using both radiology and histologic core biopsy information. Various imaging modalities such as time-dependent contrast phases were attempted to distinguish between nodular and

pseudonodular, but to no avail. To further investigate the possibility of radiologically differentiating nodules from pseudonodules, we are currently studying the use of novel MRI contrast agents.²⁴

Recognizing the different growth patterns of metastatic UM in the liver has important clinical implications. Histologically, nodular and infiltrative types exhibit differences in the host immune response: there are natural killer cells in the infiltrative form, while the nodular form contains cytotoxic T-lymphocytes.¹¹ There are also discrepancies in the formation of collagen, angiogenesis, and other factors that distinguish these two histologic growth patterns.²⁵ The choice of treatment regimens in the future may be altered due to these differences. Dayani and co-workers distinguished between infiltrative and nodular patterns of metastatic UM on hepatic angiography and noted that it can be used to predict response to hepatic arterial chemoembolization.¹⁵ Halenda and co-workers also noted that radioembolization was effective in treating nodular liver metastases, but not infiltrative sinusoidal metastases.¹³ In that particular study, a patient had a mixture of nodular and infiltrative liver metastases demonstrated by MRI. The nodular liver metastases decreased in size with radioembolization, but the infiltrative metastases did not respond to treatment and the patient ultimately progressed. Sharma and co-workers showed that patients with angiographically determined nodular tumor appearances survived longer than patients with infiltrative lesions (621 days versus 114 days overall survival).¹⁴ Differentiating between these patterns on scans is an important consideration when determining the treatment plan for patients with metastatic UM.

It is possible that the nodular pattern on imaging may represent an earlier pattern of disease that transforms into infiltrative pattern as the tumor escapes from the portal triad. Eight of our patients initially had nodular lesions that converted to infiltrative lesions on later imaging. However, we did not observe any patients whose infiltrative lesions subsequently converted to nodular lesions. These transitions may result from differences in tumor genetics that impart different behavioral and growth kinetics and/or properties within the liver itself. This is supported by the fact that primary UM can be grouped into two distinct molecular classes that exhibit differential gene expression.^{26,27} Class 1 UM (low grade) versus Class 2 (high grade) are highly predictive of patient mortality.^{28,29} Additionally, there is experimental evidence that downregulation of host natural killer cells results in an infiltrative growth pattern³⁰ and downregulation of hepatocyte pigment epithelium derived factor (PEDF) promotes the nodular growth pattern.³¹ Further investigations are needed to examine whether these genetic signatures and host microenvironmental factors are predictive of the observed growth patterns.

Metastatic UM is not the only malignancy that demonstrates different growth patterns in the liver. Several studies have demonstrated that colorectal metastases in the liver exhibit different histological patterns.^{32,33} Vermeulen et al. examined the metastatic growth for colorectal carcinoma in the liver and ultimately classified the growth patterns into three categories: desmoplastic, pushing, and replacement. The ‘pushing’ (effacing) pattern exhibited by colon cancer resembles the nodular form of UM metastasis; the tumor-liver interface was distinct and the liver was pushed aside, running in parallel with the border of the metastasis. The ‘replacement’ (infiltrative) pattern shows replacement of the liver cells

by tumor cells while retaining the original reticulin structures of the liver parenchyma; it correlates with the stage I and stage II infiltrative pattern in UM. The ‘desmoplastic’ pattern not only replaces the liver cells in the lobule, but also obliterates the reticulin structure within the liver parenchyma. It correlates with the stage III infiltrative pattern of metastatic UM.³⁴

A limitation of our study is that biopsy samples of only nine patients could be matched with the MRI appearance of single metastatic lesions. It would have been helpful to have more samples for each of the histologic patterns. However, we were able to determine that MRI nodular metastases can be infiltrative on histologic examination, and this pattern results in what we term a pseudonodule.

In conclusion, we have shown that metastatic UM exhibits two distinct growth MRI imaging patterns: nodular and infiltrative. The MRI nodular pattern corresponds to a nodule or pseudonodule formation, the latter being a form of the histologic stage II or stage III infiltrative pattern which replaces the hepatic lobule, while the MRI infiltrative pattern corresponds to the stage I histologic infiltrative pattern. Investigations are needed to determine whether imaging techniques can better distinguish between nodules and pseudonodules since the treatments may vary according to growth pattern of these hepatic metastases. In the interim, liver core biopsies are a valuable tool determining metastatic UM hepatic growth pattern and developing treatment plans. for

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Metastatic UM in liver high T1 signal. T1 axial image through liver demonstrates multiple foci of hyperintensity involving both lobes of the liver due to melanin (arrows)

Figure 2.

Metastatic UM in liver with peripheral enhancement. (A) Pre-contrast T1 weighted image demonstrates hypointense nodule in the right hepatic lobe (dashed arrow) (B) Post-contrast arterial phase demonstrates enhancement of the periphery of the lesion along with enhancement of the adjacent liver parenchyma likely due to desmoplastic reaction and/or angiogenesis (long arrow). A feeding hepatic artery is also noted (short arrow).

Figure 3.

Metastatic UM in liver MRI infiltrative pattern. (A) Axial T2-weighted image through liver demonstrates large area of increased T2 signal involving the right hepatic and caudate lobes (arrow). (B) Pre-contrast T1-weighted image demonstrates areas of T1 hyperintensity due to melanin (arrows). (C & D) Following contrast administration, the arterial phase shows avid enhancement of the lesion which is infiltrating the right hepatic and caudate lobe without defined boundaries. Delayed phase shows progressive enhancement of the metastatic uveal melanoma lesion.

Figure 4. Metastatic UM in liver MRI nodular pattern. (A) Axial T2-weighted image through liver demonstrates multiple T2 hyperintense nodules involving all lobes of the liver (arrows). (B) Pre-contrast T1-weighted image demonstrates multiple T1 hypointense nodules throughout the liver parenchyma (arrows). (C) Following contrast administration, the arterial phase shows avid enhancement of the nodules and corresponding delayed phase (D) shows wash-out of these nodules. The findings are consistent with the nodular pattern of uveal melanoma metastatic disease.

Figure 5.

Metastatic UM in liver histologic infiltrative stage I pattern. (A) The normal hepatic lobular parenchyma is infiltrated with small nodules of tumor. (B) A reticulin stain (black) highlights the sinusoidal spaces. (C) An HMB45 stain (red) shows multiple micrometastatic melanoma foci (red). (D) The micrometastases are composed of small islands of melanoma (<50µm diameter, arrows) in the sinusoidal spaces; the intervening hepatocytes are intact. (A. hematoxylin and eosin 25×; B. reticulin 25×; C. HMB45, peroxidase-anti peroxidase 100×; D. hematoxylin and eosin 100×)

Figure 6.

Metastatic UM in liver histologic infiltrative stage II pattern. (A) The micrometastatic melanoma has now expanded in the sinusoidal spaces; hepatocytes are absent and strands of collagen remain. (B) An HMB45 stain (red) highlights the islands of metastatic melanoma. (C) There are strands of collagen (*) from the residual architecture of the hepatic lobule and there are pseudosinusoidal spaces (arrow) present. (D) A CD31 stain highlights residual endothelial cells; pseudosinusoidal spaces (arrow) are also present. (A. hematoxylin and eosin 25 $\times$; B. HMB45 peroxidase anti-peroxidase 100 $\times$; C. hematoxylin and eosin 100 $\times$; D. CD31 peroxidase anti-peroxidase 100 $\times$)

Figure 7. Metastatic UM in liver histologic infiltrative stage III pattern. (A) Islands of melanoma have now nearly completely replaced the hepatic lobule; only small strands of collagen remain. (B) A CD31 stain demonstrates residual endothelium from the sinusoidal spaces. (C) There are slit-like pseudosinusoidal spaces present (arrow) and only small strands collagen (asterisk) from the collapsed lobular architecture remain. (D) There are CD31+ (red) endothelial cells present. (A. hematoxylin and eosin, 25×; B. CD31 peroxidase anti-peroxidase 100× ; C. hematoxylin and eosin 100×; D. CD31 peroxidase anti-peroxidase 100×)

Figure 8.

Metastatic UM in liver histologic nodular pattern. (A) A nodule of melanoma with interspersed vascular channels is present; note the lack of lobular architecture including the lack of intervening collagen strands. (B) A CD35 immunostain is positive (red) vascular channels in the nodule of melanoma. (C) There are CD105+ vessels in the nodule of tumor (green, arrow). (D) The CD105+ vessels are lined by endothelium (green, arrows). (A. hematoxylin and eosin, 25 $\times$; B. CD31 peroxidase anti-peroxidase 25 $\times$; C. CD105 with propidium iodine counterstain, immunofluorescence 25 $\times$; D. CD105 with propidium iodine counterstain, immunofluorescence bar=50 μ m)

Figure 9.

Diagram of sinusoidal (infiltrative) and periportal (nodular) growth patterns of metastatic uveal melanoma to the liver. In the sinusoidal (infiltrative) pattern, stage 1 includes multiple up to 50 μ m in diameter islands of tumor cells within the sinusoidal spaces resulting in an MRI infiltrative image; in stages 2–3, the islands of tumor measure between 50–500 μ m diameter and >500 μ m, respectively, and eventually take over the hepatic lobule; the stage 2–3 infiltrative pattern results in a nodular MRI image. In the periportal (nodular) growth pattern, tumor cells co-opt portal venules, grow in the space surrounding the portal triad and efface (push aside) the adjacent hepatocytes; stage 1 tumor collections <50 μ m in diameter; stage 2, 50–500 μ m and stage 3, >500 μ m diameter; the stage 2–3 nodular pattern results in a nodular MRI image.