

Case Report
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From Headaches to Obstructive Ileus: Following the Dots

C Korres, A Doukopoulos and C Triantopoulou*

Radiology Department, Konstantopouleio Hospital, Athens, Greece

***Corresponding author**

C Triantopoulou, Radiology Department, Konstantopouleio Hospital, Athens, Greece.

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Meningioma and colorectal cancer can co-exist in the same patient and may share mutations in common genetic loci and similar cell-cycle regulating proteins in comparable mechanisms of action.

Introduction

Meningioma is considered the most frequently encountered intracranial tumour, one weighing towards the elder scale of age [1, 2]. Dependent on its specific location and the consequent mass effect, it can present with numerous varying symptoms ranging from dizziness and headaches to anosmia and paresis or can even be asymptomatic [3, 4]. It is mostly a benign entity which can, nevertheless, assume more aggressive characteristics [1]. It may be a part of familial disorders, but it is most often encountered sporadically as an incidental finding [5]. Though rather remote from and decisively distinct to the gastrointestinal tract, meningioma occurrence has been linked to the co-occurrence of another neoplasm of a less benign nature, namely the colorectal cancer (CRC) [6, 7]. The latter is considered the second most common cancer with the highest mortality rate, though its gradual progression and its relative accessibility have emphasized the importance of screening tests [8, 9]. In this study we showcase a patient who presents with headaches and obstructive ileus and is then diagnosed with mucinous CRC and meningioma and we consequently prompted to investigate the genes whose expression can be altered in both of these neoplasms.

Case History-Methods

A 78-year-old female examinee arrives at the ED with complaints of diffuse abdominal pain for the past week and reported intermittent disrupted bowel movement (i.e. inability to pass gas and faeces), which had gotten worse the last two days. Her medical history was negative for surgeries in the abdomen. Her medication list included a thiazide diuretic for blood pressure adjustment and levothyroxine for hypothyroidism, both of which had been so far closely monitored and adequately regulated. The rest of her medical history was inconsequential. The patient admitted, however, the presence of occasional headaches, a symptom which, nonetheless, was not prioritised at that point.

The clinical examination revealed abdominal distention with reduced to no bowel sounds on auscultation. A basic laboratory workup provided sodium and potassium levels at the lower range and a rising lactate level.

An exploratory laparoscopy ensued, which identified three sites of tumour involvement in the ascending, transverse and descending colon and a semi-colectomy was subsequently performed. The biopsied tissue revealed a mucinous adenocarcinoma of the colon. No metastatic loci in the lungs or abdomen were identified at this point. Due to extensive lymph node involvement, chemotherapeutic rounds were initiated.

Results/Follow-Up

Five months after establishing the diagnosis, at the first follow-up, our patient presents with elevated tumour markers (*CA 19-9*: 125 U/mL and *CEA*: 135 µg/L).

An abdominal MRI pictured multiple foci in the liver highly suspicious and typical of metastases (Figure 1).

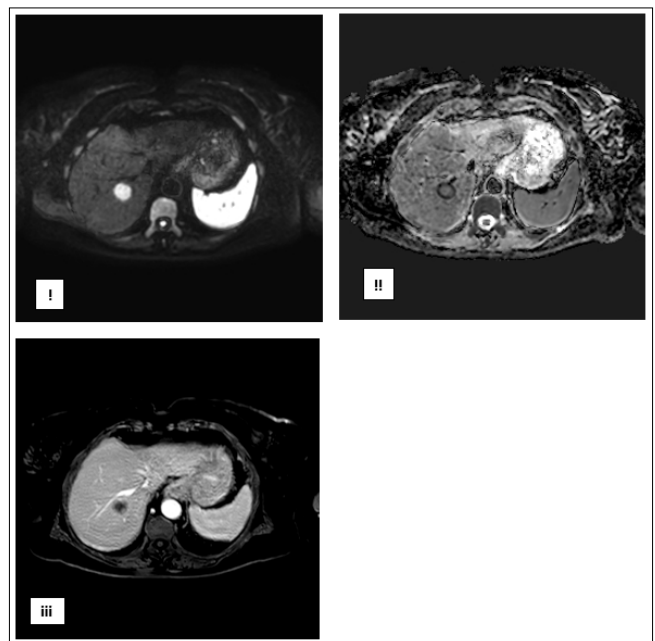


Figure 1: MRI of the Abdomen (i) DWI, (ii) ADC and (iii) after IV Contrast Enhancement.

On the hepatic segment VIII, there is a high signal lesion in (i) the DWI image which shows mostly peripheral diffusion restriction in the (ii) ADC image, while it also exhibits nodular enhancement

in the (iii) contrast enhanced phase.

However, the current main medical complaint of the patient was that of reiterative, progressively worsening headaches, which she had initially attributed to her anxiety-related trouble sleeping. Though remote to our differential list, a brain metastasis had to be ruled out.

A CT-scan of the brain was ordered and the initial images (Figure 2i) unveiled a round, well-demarcated, hyperdense mass in a frontal parafalcine location with a wide base to the underlying dura, both of which -characteristic location and NECT appearance- attributable to meningioma. After contrast administration, the above described mass exhibited uniform enhancement (Figure 2ii), further supporting our inchoate notion of the mass as a meningioma. Moreover, no to minimal edema was detected on the surrounding tissue, an additional feature favouring a more benign diagnosis.

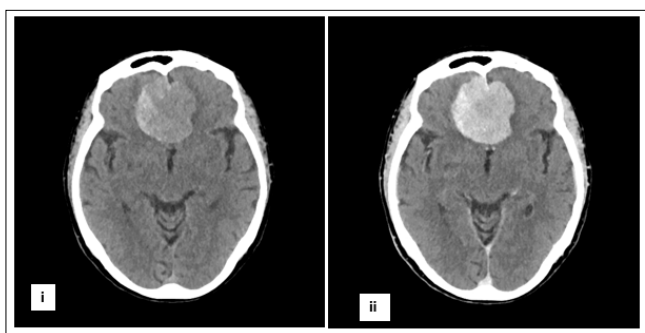


Figure 2: CT scan of the Brain without (i) and after IV Contrast Enhancement (ii)

A parafalcine, hyperdense mass is depicted in (i) with a wide base to the dura which enhances homogeneously after IV contrast injection (ii). There is only mild underlying edema of the brain parenchyma.

The patient refused to partake in an MRI scan of the brain or be subjected to brain surgery. The oncologic board, thus, decided to monitor the lesion as needed for signs of growth through CT scans, while the patient's symptoms were to be controlled with analgesic medication. At a farther follow-up three months later, the size and imaging characteristics of the dura-based mass remained unaltered (Figure 3ii) and the headaches were sufficiently managed.

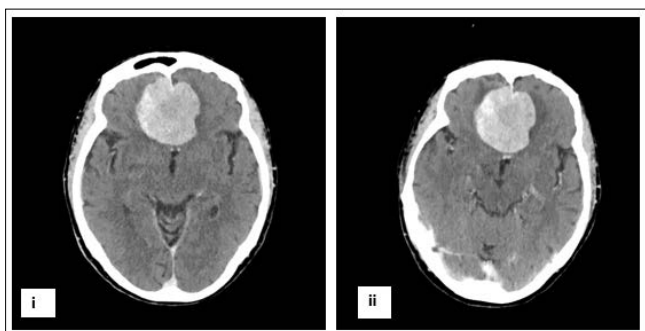


Figure 3: Contrast-enhanced CT scan of the Brain (i) at the First Evaluation and (ii) three Months Later.

The parafalcine mass 3 months later after the first imaging, exhibits the same morphology, size and homogeneous enhancement, with mild surrounding edema, in accordance to a meningioma quiddity.

In the meantime, and after another chemotherapeutic cycle, an abdominal MRI scan was anew performed to our patient in order to assess the progression of the liver lesions. The latter showed signs of significant size-reduction (Figure 4ii).

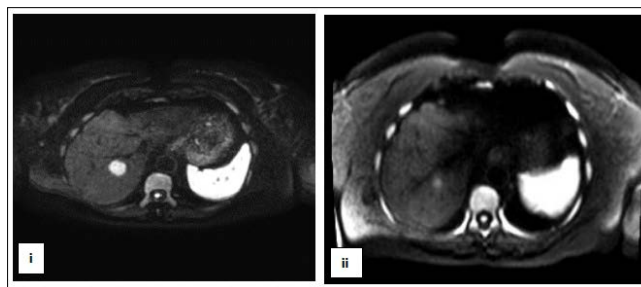


Figure 4: DWI-MRI of the abdomen (i) at the first follow-up and (ii) three months later.

The high-signal lesion on the hepatic segment VIII in the DWI parameter image is markedly decreased in (ii) three months later after the initial follow-up.

Discussion

The quintessence of our study is to explore the potential relation in a genetic -and sequentially, protein- level between the parallel presence of meningioma and colorectal cancer at the span of one's lifetime.

The most common genetic alterations that are encountered in a meningioma comprise those on the Neurofibromatosis 2 gene (NF2) on chromosome 22 [10-13]. The end-product of this gene is a tumour-suppressing protein, highly producible in the nervous system, especially the Schwann cells, named merlin, whose loss of function also drives meningioma formation [12, 13]. Similarly, studies on colorectal cancer have indicated that high-grade colorectal carcinomas showed poor NF2/merlin expression, especially compared to vicinal healthy cells, while exhibiting an analogous poor prognosis, thus showcasing the possible importance of NF2 in the feasible co-existence of the neoplasms concerned [14, 15].

Akt1 consists another gene implicated in both meningioma and colorectal cancer involvement. It is a serine/threonine kinase and has a key role in the progression of the cell cycle from G0 to G1/S promoting cell proliferation and therefore acting as an oncogene. Regarding meningioma, the end-result of Akt1 is osteoglycin, an oncogenic protein [16-18]. Osteoglycin has been shown to drive meningioma proliferation via downregulation of the aforementioned NF2 gene and through upregulation of the mTOR signalling pathway, which in turn is implicated farther in cell proliferation and tumour metabolism and has been for this reason a luring anti-tumour target [19-22]. Interestingly, Akt1 can have a dual effect in colorectal cancer. It is upregulated in carcinogenic cells, in an analogous way to the progression of the disease and negatively impacts possible chemo-treatments, by inducing antiapoptotic agents, such as NF- κ B [21]. On the other hand, however, it may pause cellular adhesion and hence metastatic disease in the colonic cells [22]. This is achieved via inhibition of the transcriptive functions of NFAT, which has stem-cell effects, controls cell proliferation and survival and partakes in epithelial-to-mesenchymal transition [23, 24]. The effects of NFAT extend to downregulation of E-cadherin, a cellular adhesion molecule with tumour-suppressing qualities [25]. Thus, the inhibition of NFAT by Akt1 results in upregulation of the onco-suppressing E-cadherin and the metastatic motility of the CRC is reduced

[25]. Nevertheless, it has been connected to a higher recurrence rate in meningioma, conceivably via its antiapoptotic esse [13].

Higher on the aforementioned signalling pathway chain stands another oncogene, namely the PIK3CA, which expresses a protein that partakes in the phosphatidylinositol 3-kinase (PI3K) [16]. This enzyme phosphorylates and, ergo, activates the Akt1, among other targets, and drives its expression [13, 16]. It may, consequently, be found increased in both meningioma and colorectal carcinoma, and drives in fact a higher-grade stage and a less favourable prognosis [26-28]. Additionally, PIK3CA has been discovered more often upregulated in mucinous among CRC types, alone or in association to the oncogene KRAS which also poses a higher incident of mutations in mucinous CRC and may be involved with the PIK3CA/Akt1 pathway [27, 29].

Although not necessarily affecting the same gene loci, epigenetics, especially in the form of CpG islands seem to hold an important role in both types of neoplasm discussed here [30-32]. CpG aberrant methylation is linked to instability of the genome and even silencing of certain genes that are pertinent to cell survival and proliferation or evasion from the immune system, that is decidedly associated to a higher-grade, therapy-resistant and recurrence-prone tumours [31-33]. The Krueppel like factor 4 (KLF4) gene is one such example of epigenetic alteration that has been ascertained hypermethylated in both CRC and meningiomas [13, 16, 34]. As a tumour-suppressive transcription regulator KLF4 can determine tumour occurrence and progression separately from its epigenetic-induced role via individual mutations which comparably seem to affect its expression via inhibition [16, 34]. Consequently, epigenetics and its potential early links to genomic stability and programmed function could assume a critical part in predicting if not even ab initio preventing the extant of the pertained neoplasms. Though advised to a genetic testing, our patient's wishes were to be no farther involved in additional examinations.

Our main account of the patient's brain finding was that it consisted a meningioma. It is in our understanding, however -and lies within the limitations of this study- that a definitive meningioma diagnosis could be more safely advocated through an MRI examination or, decisively via a histopathologic result. The possibility of a metastatic intracranial lesion or even a secondary-to-primary neoplasm infiltration (i.e. metastatic disease that develops in the primary meningioma tumour), though considered remote cannot, however, be completely dismissed [35-37]. It has been corroborated that even a metastatic brain neoplasm can manifest characteristics similar to a meningioma, thus, taking the name of "meningioma-mimic" [36, 37]. It has also been evinced that even if infrequent, it is nonetheless, plausible for a primary colorectal neoplasm to metastasise in a pre-existing primary brain meningioma [37].

Nevertheless, some imaging characteristics of the brain lesion discussed here, strongly drive the diagnosis to the more benign meningioma verdict. The homogeneous enhancement, the central position of the mass and the lack of excessive surrounding edema, the consistency of those findings and the constant size of the mass in the follow-up study all compose both separately and together solid evidence towards a meningioma interpretation [35, 36]. This exposition can be further elucidated, though by no means substantiated, by both the very rarity of a primary gastrointestinal tumour metastasising to the intracranial fossa [38, 39], as well as the meningioma-inclined position in a parafalcine location [4].

In conclusion, prompted by the case of a patient with meningioma and concurrent colorectal cancer, we sought to explore the possible genetic information and common mechanisms that could drive these different entities into synchronous actualization. We present some proteins that are common in both types of neoplasms and act mostly in a kindred manner, mainly through hindering apoptosis and favouring cell-proliferative pathways.

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