Pneumatosis intestinalis in a radioactive iodine-refractory metastasic thyroid papillary carcinoma with BRAF<sup>V600E</sup> mutation treated with dabrafenib–trametinib: a case report

M. C. Martín-Soberón¹*, S. Ruiz², G. De Velasco¹, R. Yarza¹, A. Carretero¹, D. Castellano¹ and J. M. Sepúlveda-Sánchez¹

Abstract
Background: Pneumatosis intestinalis (PI) is a rare entity which refers to the presence of gas within the wall of the small bowel or colon which is a radiographic sign. The etiology and clinical presentation are variable. Patients with PI may present either with chronic mild non-specific symptoms or with acute abdominal pain with peritonitis. Some cases of intestinal pneumatosis have been reported as adverse events of new oncological treatments such as targeted therapies that are widely used in multiple tumors.

Case presentation: A 59-year-old caucasian female with radioactive iodine-refractory metastatic thyroid papillary carcinoma with BRAF<sup>V600E</sup> mutation was treated with dabrafenib and trametinib as a compassionate use. After 4 months treatment, positron emission tomography–computed tomography (PET–CT) showed PI. At the time of diagnosis, the patient was asymptomatic without signs of peritonitis. The initial treatment was conservative and no specific treatment for PI was needed. Unfortunately, after dabrafenib–trametinib withdrawal, the patient developed tumor progression with significant clinical worsening.

Conclusions: This case report is, in our knowledge, the first description of PI in a patient treated with dabrafenib–trametinib. Conservative treatment is feasible if there are no abdominal symptoms.

Keywords: Case report, Pneumatosis intestinalis (PI), Targeted therapies, Dabrafenib, Trametinib, Thyroid cancer

Background
Pneumatosis intestinalis is a rare condition characterized by the presence of subserosal and submucosal gas, with air-filled cysts occurring anywhere in the gastrointestinal tract [1]. PI often presents as an incidental finding on abdominal imaging in asymptomatic patients, but it may occur in the context of life-threatening intestinal pathology, such as acute intestinal ischemia [2]. The pathogenesis is poorly understood and PI is associated with a wide range of etiologies. Chemotherapy has been defined as a well-known predisposing factor by oncologists [3]. Nowadays, due to the increased use of targeted therapies, PI has also been described as a side effect of multiple targeted anticancer drugs [4]. This entity is one of the few conditions where a pneumoperitoneum has no mandatory indication for laparotomy [5]. Although the association of tyrosine kinase inhibitors with PI is rare, its knowledge and management are essential in the era of these targeted therapies.

*Correspondence: mcms.207@gmail.com
1 Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain
Full list of author information is available at the end of the article

© The Author(s) 2021. Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.
Case presentation

A 59-year-old caucasian female was diagnosed with thyroid papillary carcinoma after total thyroidectomy in 2001. Diagnosed with postsurgical hypothyroidism under treatment with levothyroxine, 100 micrograms per day. There was no other previous medical history of interest. The patient did not consume tobacco or alcohol.

In 2008, a computerized tomography scan (CT) showed locoregional relapse and surgery was performed with resection of locoregional recurrence and left cervical lymphadenectomy. In November 2011, pulmonary relapse was treated with 1-131 since November 2011 until March 2012 (total accumulated dose: 850 mCi). In October 2016, a CT scan showed a progression of the disease with cervical and pulmonary progression. The patient started sorafenib, 400 mg twice a day. Stable disease was maintained during 20 months. In June 2018, patient presented an episode of abrupt instability and cervical pain. The magnetic resonance imaging (MRI) (Fig. 1) showed a new metastatic lesion in the skull base with destruction of bony structures of the left occipital-petrous region.

At this point, a molecular study of the cervical node was performed and a mutation in **BRAFV600E** was found.

Due to the lack of alternative therapeutic options, treatment with vemurafenib–trametinib was requested as a compassionate use. In August 2018, patient was started on the combination of dabrafenib 150 mg twice a day and trametinib 2 mg once a day. MRI in October 2018 showed a slight decrease of the metastatic lesion in the skull base (Fig. 2). In addition, the patient showed evident clinical improvement with decreased initial headache and cervicalgia.

A follow-up PET–CT scan was performed in January 2019. Tumor was on radiological partial response. In addition, there was intestinal pneumatosis with mild sign of pneumoperitoneum (Fig. 3). Patient had no digestive symptoms and the abdominal medical examination was completely normal. Also normal neurological examination was verified. Routine physical examination showed blood pressure 110/60 mmHg, heart rate 80 bpm and 36.5 degree centigrade temperature. Blood test showed normal liver function: AST 21 U/L, ALT 16 U/L, bilirubin 0.19 mg/dL and normal renal function: creatinine 0.7 and glomerular filtrate > 90 mL/min. Blood count values were normal: leukocytes 7.6 × 1000/µL, hemoglobin 12 g/dL and platelets 417 × 1000/µL.

The surgery department recommended conservative treatment unless new abdominal signs or symptoms were seen. Intravenous metoclopramide 10 mg/8 h and paracetamol 1000 mg/8 h were administrated. Both drugs, dabrafenib and trametinib, were discontinued after the PI diagnosis.

Only 10 days after the discontinuation of targeted therapy, tumor progression was shown with clinical deterioration due to intracranial hypertension and the patient died 4 weeks later because of intracranial disease progression. Because the cause of death was related with tumor progression, autopsy was not performed.

Discussion

Despite PI being related to targeted therapies, we have not found any report in patients receiving dabrafenib–trametinib. Here, we presented a case of a 59-year-old...
woman who developed PI 5 months after starting the combination treatment with those drugs. Papillary thyroid cancer is the most common type among all thyroid tumors. Outcome of refractory radioactive iodine tumors is poor, the 10-year survival is 10% from the time of detection of metastasis [6]. About half of papillary thyroid cancers harbor the \( \text{BRAF}^{V600E} \) mutation. Although the value of this mutation is still under investigation, thyroid cancer harboring \( \text{BRAF}^{V600E} \) mutation have worse prognosis [7]. In the last decade, tyrosine kinase inhibitors have been approved and used for radioactive iodine-refractory patients.

Vemurafenib and dabrafenib potently inhibit \( \text{BRAF} \) proteins containing the \( V600E \) mutation and are indicated for patients with non-resectable or metastatic melanoma associated with this mutation [8]. Both drugs act in the \( \text{RAS}–\text{RAF}–\text{MEK}–\text{ERK} \) pathway which is overactivated by oncogenic mutation in the \( \text{BRAF} \) protein, triggering overactivation of this pathway and increasing cell proliferation, cell survival and angiogenesis [9]. Dabrafenib inhibits mutated \( \text{BRAF} \) proteins and trametinib inhibits \( \text{MEK} \). Neither dabrafenib nor trametinib is currently approved for papillary thyroid cancer, however responses have been observed to those drugs in thyroid tumors carrying the \( \text{BRAF}^{V600} \) mutation.

In the last decade, the extended use of those targeted therapies has caused new types of toxicities. PI is a multifactorial entity with a wide range of etiologies: changes of the intestinal wall, peritonitis, bowel distention and corticosteroid therapy are some of the described etiologies [10].

A wide study evaluating the association of targeted therapies with PI and bowel perforation was published by Shinagare AB et al. These authors retrospectively
reviewed 48 patients with cancer who developed one of these abdominal complications. Twenty-four patients were receiving molecular targeted therapies and have no other risk factors for PI or bowel perforation. Investigators showed that bevacizumab ($n=14$) and sunitinib ($n=6$) were the most common drugs associated with PI. Other drugs included were sorafenib, cetuximab, erlotinib and ipilimumab [11]. In the context of those treatments, the precise mechanism that leads to the association between targeted therapies and PI is currently unknown. In the case of antiangiogenics, bevacizumab, an anti-VEGF monoclonal antibody, has been shown to compromise the bowel wall integrity, producing intestinal wall disruption due to necrosis of the serosa and PI [11].

**Conclusion**

Despite the existence of other targeted therapies associated with PI, to our knowledge, this is the first report of PI in a patient receiving dabrafenib–trametinib. Conservative treatment is feasible if there are no abdominal signs or symptoms. However, the discontinuation of the cancer treatment led to a clinical deterioration and progression of the thyroid cancer. Understanding the toxicity of novel treatments is crucial in the management of our patients. In patients who are receiving targeted therapies it is possible that PI, if it appears, determines the vital prognosis and it should be considered a severe adverse event.

**Abbreviations**

PI: Pneumatosis intestinalis; PET–CT: Positron emission tomography–computed tomography; CT: Computed tomography; MR: Magnetic resonance imaging; VEGF: Vascular endothelial growth factor.

**Acknowledgements**

Not applicable.

**Authors’ contributions**

All authors have approved the manuscript, including the conflict of interest statements, for submission for publication. All the authors have been involved in review of previous bibliography and review of successive drafts of the manuscript and have approved the manuscript.

**Funding**

There was no funding received for this project.

**Ethics approval and consent to participate**

This case report study was carried out respecting the Declaration of Helsinki in its current version. The study of a case report is exempt from ethical approval in our institution.

**Consent for publication**

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

**Availability of data and materials**

This case report corresponds to a real case diagnosed and treated in our clinical center. Clinical and radiological data presented correspond to real data.

The datasets supporting this article are stored in Hospital 12 Octubre medical records.

**Competing interests**

The authors included in this case report declare that they have no conflict of interest.

**Author details**

$^1$ Medical Oncology Department, University Hospital 12 de Octubre, Madrid, Spain. $^2$ Nuclear Medicine Department, University Hospital 12 de Octubre, Madrid, Spain.

Received: 10 June 2019 Accepted: 11 November 2020 Published online: 02 March 2021

**References**

1. Yale CE, Balish E. Pneumatosis cystoides intestinalis. Dis Colon Rectum. 1976. https://doi.org/10.1007/BF02590860.
2. Koss LG. Abdominal gas cysts (pneumatosis cystoides intestinalorum hominis); an analysis with a report of a case and a critical review of the literature. AMA Arch Pathol. 1952;53(6):523–49.
3. Vargas A, Pagès M, Buixà E. Pneumatosis intestinalis due to 5-fluorouracil chemotherapy. Gastroenterol Hepatol. 2016;39(10):672–3. https://doi.org/10.1016/j.gastrohep.2015.09.010.
4. Shinagare AB, Howard SA, Krajewski KM, Zukotynski KA, Jagannathan JP, Ramaiya NH. Pneumatosis intestinalis and bowel perforation associated with molecular targeted therapy: an emerging problem and the role of radiologists in its management. AJR Am J Roentgenol. 2012a;199(6):1259–65. https://doi.org/10.2214/AJR.12.8782.
5. Dhadlile S, Mehanna D, McCourtney J. Pneumatosis intestinalis a trap for the unwary: case series and literature review. Int J Surg Case Rep. 2018;53:214–7. https://doi.org/10.1016/j.ijscr.2018.10.079.
6. Durante C, Haddy N, Baudin E, Lebouilleux S, Hartl D, Trivaglio JP, Caillou B, Ricard M, Lumbroso JD, De Vathaire F, Schlumberger M. Long-term outcome of 444 patients with distant metastasis from papillary and follicular thyroid carcinoma: benefits and limits of radioiodine therapy. J Clin Endocrinol Metab. 2006;91(8):2892–9 (epub 2006 May 9).
7. Iva J, Filip G, Martin B, Pavel Z, Jan C. The significance of BRAFV600E mutation in thyroid cancer terms of novel targeted therapies—overview of current knowledge and studies. Klin Onkol Fall. 2018;31(5):339–44. https://doi.org/10.1055/s-0038-1668662.
8. Robert C, Karasiewska B, Schachter J, Rutkowski P, Mackiewicz A, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;372(1):30–9. https://doi.org/10.1056/NEJMoa1412690.
9. Rissmann R, Hessel MH, Cohen AF. Vemurafenib/dabrafenib and trametinib. Br J Clin Pharmacol. 2015;80(4):765–7. https://doi.org/10.1111/bcp.12651.
10. Sebastià C, Quiroga S, Espin E, Boyé R, Alvarez-Castells A, Armengol M. Portomesenteric vein gas: pathologic mechanisms, CT findings, and prognosis. Radiographics. 2000;20(5):1213–24 (discussion 1224–1226).
11. Shinagare AB, Howard SA, Krajewski KM, Zukotynski KA, Jagannathan JP, Ramaiya NH. Pneumatosis intestinalis and bowel perforation associated with molecular targeted therapy: an emerging problem and the role of radiologists in its management. AJR Am J Roentgenol. 2012b;199(6):1259–65. https://doi.org/10.2214/AJR.12.8782.

**Publisher's Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.