case report

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Immunotherapeutic approach to a case of advanced hepatoid adenocarcinoma of the lung

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Summary
Rationale Hepatoid adenocarcinoma (HAC) is an extrahepatic primary tumor that expresses morphological features resembling hepatocellular carcinoma. This rare malignant tumor has been described in the gastrointestinal (GI) tract, the testes, the ovaries, and rarely, the lungs. Despite there being no standardized management protocol for this case with poor prognosis, the literature describes responses to treatment with cisplatin–etoposide chemotherapy.
Objective We present an updated review of all cases of HAC of the lung and the favorable results of a novel management method for this type of tumor.
Results A table including all the HAC of the lung cases on the electronic database PubMed since 1980 is compiled. Here we present a case of primary HAC of the lungs, initially managed with cisplatin–etoposide without favorable response to treatment. The immunohistochemical profile of the tumor allowed for the novel use of immunotherapy in the setting of primary lung HAC, with favorable response.
Conclusion and outlook The case presented here is of interest as it adopts a novel immunotherapeutic approach to HAC, yielding a promising outcome. This highlights the importance of molecular typing and immunohistochemical profiling in the diagnosis and management of non-small cell lung cancer.

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Abbreviations

AFP	Alpha fetoprotein
CDX	Caudal type homeobox
CEA	Carcinoembryonic antigen
CK	Cytokeratin
HAC	Hepatoid adenocarcinoma
HCC	Hepatocellular carcinoma
PAX	Paired box gene
PSA	Prostate-specific antigen
TTF	Thyroid transcription factor

Introduction

Hepatoid adenocarcinomas (HAC), first described in 1985 by Ishikura et al. [1], are a rare type of extrahepatic alpha-fetoprotein secreting tumor with hepatocellular carcinoma (HCC) like morphology. Since that time, only 33 cases of HAC of the lung have been published in PubMed, and the main features of all these cases are summarized in Table 1.

Two criteria are usually described for the diagnosis of hepatoid adenocarcinoma, the first being a mixture of tubular or papillary adenocarcinoma with sheet-like or trabecular proliferation of neoplastic cells within an AFP-producing carcinoma. The second criterion is cells with abundant, eosinophilic cytoplasm and centrally located nuclei, in the sheet-like or trabeculated portion [2]. The immunohistochemical profile of HAC tumors has shown to be variable. It has been found that 91.6% of HAC tumors stain positive for AFP [3, 4].

Primary HAC of the lung comprises 5% of all reported cases of hepatoid adenocarcinoma, with the stomach being the most common site of occurrence [5]. The literature shows that 100% of HAC stain pos-

Table 1 Summary of previously reported cases of hepatoid adenocarcinoma of the lung. Table compiled from adaptation of Grossman, Beasley and Braman (2016) and a PubMed search (keywords: Hepatoid adenocarcinoma AND Lung between June 2015 and present)

Autor	Publication year	Age (years)	Gender	Location	Size (cm)	Smoker	AFP level (ng/uil)	Stage	Progression	Treatment
Yasunami et al. [7]	1981	67	Male	Left Upper Lobe	"Fist-sized"	Not given	19,000	pT3 N2	Rib and vertebra metastases	XRT, Immuno tx (BCG)
Yokoyama et al. [8]	1981	69	Male	Right Lower Lobe	11 × 11 × 7	Not given	5050	pT3 M1b	Not applicable	N/A
Miyake et al. [9]	1986	40	Male	Right Upper Lobe	8 × 9 × 7	Not given	3090	pT3M1b	Not applicable	Surg
Miyake et al. [9]	1986	55	Male	Right Upper Lobe	5	Not given	2123	pT2a M1b	Not applicable	Surg
Miyake et al. [10]	1987	73	Male	Left Upper Lobe	5 × 6 × 5	Not given	1039	pT2b N2	Mediastinal, LN, brain metastases	Surg, XRT
Okunaka et al. [11]	1992	49	Male	Right Upper Lobe	6 × 5 × 5	Not given	9300	eT3	No progression at 11 months	Surg
Arnould et al. [2]	1997	36	Male	Left Upper Lobe	10	Yes	11,600	pT4 N2	Brain Metastasis	Chemo, Surg
Nasu et al. [12]	1997	63	Male	Right Upper Lobe	14 × 13 × 12	Not given	14,000	cT4 N2	Lung, right adrenal, brain metastases	Chemo
Carlinfante et al. [13]	2000	82	Male	Left Lower Lobe	3.5	Yes	Not Assayed	cT2a N0 M0	No progression 7 years after surgery	Surg
Genova [14]	2002	71	Male	Left Upper Lobe	7.7 × 6.4	Not given	Not Assayed	pT3 N0	No progression at 24 months	Surg
Hayashi et al. [15]	2002	55	Male	Right Upper Lobe	5 × 4.8 × 6.5	Yes	89	pT2b N0	No progression at 32 months	Surg
Hiroshima et al. [16]	2002	71	Male	Right Lower Lobe	10.5 × 8.5 × 7	Yes	7417	pT3 N1	Lung and brain metastases	Surg
Iino et al. [17]	2003	63	Male	Right Upper Lobe	2.8 × 2.5	Not given	N/A	cT1 N0 M0	No progression 5 months after surgery	Surg
Oshiro et al. [18]	2004	77	Male	Right Lower Lobe	Not Reported	Not given	Not Assayed	cT2 N0 M0	Liver metastasis	Surg
Ivan et al. [19]	2007	54	Male	Left Upper Lobe	13 × 11	Yes	14,540	pT4 N3 M1	N/A	Chemo, XRT
Kishimoto et al. [20]	2008	64	Male	Left Lower Lobe	7.5 × 7 × 4	Not given	673	cT3 N0 M0	Not reported	Surg
Kim et al. [21]	2009	49	Male	Left Upper Lobe	6	Not given	14,707	pT2b N1	Not reported	Surg
Valentino et al. [22]	2012	71	Male	Right Lower Lobe	1.8 × 1.5 × 1.5	No	34,791	pT1 N0 M1	Died 4 months after presentation	Chemo, XRT, Surg
Lin et al. [23]	2013	66	Male	Right Upper Lobe	7.4 × 6 × 4.8	Yes	8686	cT3 N2 M0	Alive 57 months after presenting	Surgery, adjuvant chemo
Haninger et al. [24]	2014	51	Male	Right Upper Lobe	4.2 × 3.7	Yes	1.3 (post-tx)	cT2a N3 M1b	Died 14 months after presentation	Chemo, XRT, Surg

Table 1 (Continued)

Autor	Publication year	Age (years)	Gender	Location	Size (cm)	Smoker	AFP level (ng/uil)	Stage	Progression	Treatment
Haninger et al. [24]	2014	52	Male	Right Upper Lobe	2.5	Yes	Not Assayed	cT1b N0 M1b	Alive 37 months after presented	Surg, Chemo, XRT
Haninger et al. [24]	2014	64	Male	Left Upper Lobe	3.2 × 2.2	Yes	1 (post-tx)	cT2a N0 M1b	Died 10 months after presentation	Surg, Chemo, XRT
Haninger et al. [24]	2014	54	Female	Left Upper Lobe	1	Yes	Not Assayed	cT1a N0 M1b	Alive 9 years after presentation	Chemo, XRT, Surg
Haninger et al. [24]	2014	60	Male	Right Upper Lobe	11.2 × 10.1 × 8.5	Yes	4410	cT3 N2 M1b	Alive 1 month after presentation	Chemo, XRT
Shaib et al. [25]	2014	52	Male	Left Upper Lobe	11.8 × 12 × 8	Yes	5000	cT3 N0 M1	Alive 6–7 months after presenting	Palliative Chemo
Che et al. [26]	2014	48	Male	Left Upper Lobe	7.8 × 7.9 × 10	Yes	6283	pT4 N1 M0	Died 36 months after presentation	Chemo, XRT
Gavrancic and Park [27]	2015	64	Male	Right Upper Lobe	3.8 × 2.9	Not given	181	cT2 N2 M1	Died 11 months after presentation	Chemo, Sorafenib, XRT
Grossman et al. [5]	2016	54	Male	Right Upper Lobe/ Paratracheal	4.1 × 5.1	Yes	2	pT4 N0 M1b	Died 4 months after presentation	XRT
Qian et al. [28]	2016	79	Male	Right Parahilar	2.7 × 2.6	Yes	698	Not reported	Died 25 days after tx start by lung infection	Chemo
Motooka et al. [29]	2016	69	Male	Left Upper Lobe	4.3	Yes	4497	pT2a N0 M0	Alive 51 months after surgery	Surg, Adjuvant chemo
Sun et al. [30]	2016	59	Male	Right Upper Lobe	4.5 × 3.8 × 3.5	Yes	Not assayed	pT2a N0 M0	Alive with no recurrence or metastasis 23 months after surgery	Surg
Valle et al. [31]	2017	61	Male	Left sided	Not reported	Not given	Not assayed	Stage IV A	Further metastasis to tonsil	Chemo
Basse et al. [32]	2018	43	Not given	Right Hilar	Not reported	Yes	Not assayed	Metastatic	Died after partial immunotx response due to infectious complications	Chemo, Immuno

Tx treatment, *XRT* Radiotherapy, *Chemo* Chemotherapy, *Surg* Surgery, *AFP* Alphafetoprotein

itive for AFP, CEA, CK18 and CK19 [3]. Furthermore, a report by Shao et al. [6] extensively discusses the various management approaches used in previous cases of HAC of the lung, and concludes that an optimal regiment for the systematic treatment of advanced HAC of the lung remains elusive.

Case history

A 59-year-old African–American male presented to the emergency department with right sided chest pain of recent onset, and numbness in the right upper extremity (RUE). The patient is a former smoker with >30 pack–year history and is currently employed as a transportation supervisor. The patient's family history is significant for colon cancer in the father. A chest CT showed a 9.3 × 7.2 × 6.8 cm mass located in the upper lobe of the right lung. The mass presented with hilar lymphadenopathy. The CT scan did not exhibit contralateral adenopathy, and the CT-guided lung biopsy was inconclusive. The patient was scheduled for a repeat biopsy and a brain MRI to rule out brain metastases.

Patient underwent navigational bronchoscopy with core needle biopsy. The pathological findings were as follows: poorly differentiated carcinoma with hepatoid features. Brain MRI ruled out brain metastases. The surgical pathology report (processed at the University of Maryland Baltimore Washington Medical Center Laboratories) reads as follows:

- Fragments of lung tissue showing a poorly differentiated carcinoma consistent with hepatoid carcinoma
- Tumor cells are positive for CK7 immunohistochemical stain and negative for TTF1, CK5/6
- The PSA, CK20, CDX2, PAX8, GATA3 and PSA immunohistochemical stains are non-contributory
- Cytology specimen from 4R Lymph Node aspirate is positive for HEPAR immunohistochemical stain consistent with hepatoid carcinoma

PET-CT ruled out a primary hepatocellular carcinoma and showed a 4.6 × 4.4 cm left adrenal mass. At that time, the patient's symptomatology was significant for decreased appetite, weight loss of 2 kg, and RUE numbness. Complete blood count was normal. AFP level was 1.5 ng/ml (*reference range <10 ng/ml*). CEA level was 32 ng/ml (*reference range <3 ng/ml*). The patient was started on a combination of cisplatin and etoposide chemotherapy.

Tumor was confirmed as primary hepatoid adenocarcinoma of the lung, stage IV-A. TNM staging: $cT_4N_2M_{1b}$: metastases were found in the mediastinal and hilar lymph nodes and the left adrenal gland. The immunohistochemical profile of the tumor was obtained: histological grade 3. EGFR negative. ALK-rearrangement: negative. BRAF w/t. ROS-1: negative. MSI: unknown. PD-L1 ≥50%. The patient by that time had received two cycles of cisplatin–etoposide therapy. Symptomatology was significant for decreased appetite, weight loss of 4 kg, and myelosuppression with an absolute neutrophil count of 600 mm^3 (*reference range: 1500–8000 mm^3*). TNM stage $cT_4N_2M_{1b}$.

Patient was initiated on pembrolizumab and the combination of cisplatin–etoposide was discontinued after two cycles. Immunotherapy was well tolerated by the patient. After 3 cycles of immunotherapy, the CEA level was 5.3 ng/mL, and the complete blood count was within reference range. The patient did not suffer from electrolyte abnormalities, and gained 3 kg. After the 5th cycle of pembrolizumab, follow-up CT showed a reduction of 45% in tumor size. Symptomatology was relevant for iron-deficiency anemia which is being treated with iron supplementation. After the 10th cycle of pembrolizumab, the patient's CEA increased to 17.3. Scheduled chest CT showed progression at the primary site without evidence of progression at metastatic sites. PET-CT showed a large upper lobe mass consistent with the patient's known NSCLC primary with interval growth of lesion in the right thoracic inlet, but with decrease in size and activity of right hilar lymphadenopathy and left adrenal metastasis. Findings are consistent with a mixed response but large amount of persistent residual disease.

Patient therapy after 10 cycles of pembrolizumab has been switched to 3rd line therapy with ramucirumab and docetaxel. Patient's symptomatology is negligible.

Discussion

The diagnosis of HAC is a complicated process as it is difficult to differentiate from metastatic hepatocellular carcinoma (HCC), even in the absence of a visible primary tumor in the liver. The data in Table 1 shows that 21 of the listed patients had their AFP measured prior to the initiation of treatment. Although 20 patients presented with elevated serum AFP levels, our case and the case reported by Grossman et al. [5] showed normal serum AFP levels. As a result, serum AFP cannot be used as a diagnostic criterion for HAC. Furthermore, a study has shown that when the cut-off value is of 20 ng/ml, serum AFP has a sensitivity of 41–65% and a specificity of 80–94% [33]. This low sensitivity indicates that serum AFP level is not reliable for the detection of HCC. In the setting of an extrahepatic tumor showing hepatic-like features and an absence of a primary tumor in the liver on diagnostic imaging, the reported specificity supports the ruling out of HCC on the basis of negative serum AFP test. There have also been reports of CEA-producing HAC in the literature, but not enough evidence suggests the use of CEA levels as a diagnostic criterion. This marker can however be used in a clinical setting to monitor disease progression. This patient presented with an elevated CEA that did not change in response to treatment with cisplatin–etoposide. This was expected due to the lack of any positive response to the chemothera-

Table 2 Summary of the patient's clinical course

Date	Clinical course	AFP (ng/mL)	CEA (ng/mL)	Imaging
April 19, 2018	Prior to treatment	1.5	32.0	Chest CT showing a 9.3 × 7.2 cm mass located in the upper lobe of the right lung (RUL) PET-CT hilar lymphadenopathy and left adrenal metastasis
June 6, 2018	Status post 2 cycles of cisplatin–etoposide	1.5	31.7	N/A
August 29, 2018	Status post 2 cycles of pembrolizumab	n/a	5.7	N/A
October 10, 2018	Status post 5 cycles of pembrolizumab	n/a	5.3	Chest CT shows 45% reduction in mass
December 2018	Status post 9 cycles of pembrolizumab	n/a	6.2	N/A
January 23, 2019	Status post 10 cycles of pembrolizumab	n/a	17.3	Chest CT shows growth of primary mass in RUL PET-CT shows a RUL mass measuring 8.4 × 9.0 cm and a right thoracic inlet mass measuring 3.1 × 3.6 cm

peutic treatment. CEA levels had decreased and stabilized after switching to pembrolizumab and had been stable until December 2018, a period of 6 months. A serial rise in CEA (Table 2) prompted a CT scan which indicated progression at the primary site. This evidence is suggestive that CEA could be used to clinically monitor CEA-producing NSCLC.

The rarity of this type of tumors does not allow to define a standard treatment. There is no generalized consensus about the treatment of HAC, but based on previously published case reports, surgical resection and neoadjuvant chemotherapy is the treatment of choice for non-advanced HAC of the lung ([4]; Table 1). In the case we bring forward, the patient's stage at presentation did not make them eligible for surgery and they were thus started on cisplatin and etoposide. The use of this combination is reported as both a primary intervention in the setting of advanced disease or as neo-adjuvant therapy in the setting of a resectable tumor (Table 1).

The disappointing response to chemotherapy prompted the decision to change the treatment regimen to an immunotherapeutic agent. Pembrolizumab is a PD-L1 receptor antagonist that has been approved by the FDA for the treatment of NSCLC with high PD-L1 expression and as first line treatment of advanced NSCLC regardless of PD-L1 expression. The PD-L1^{+} immunohistochemical profile of the tumor supports the use of pembrolizumab for treatment. This is the first reported use of pembrolizumab in a case of hepatoid adenocarcinoma. We believe that this highlights the importance of immunohistochemical analysis in the management of HAC specifically, and NSCLC generally. We recommend that all patients with NSCLC be investigated for immunohistochemical markers prior to initiation of treatment, which will allow for targeted therapy. The adoption of an immunotherapeutic treatment regimen has allowed for a treatment course less burdened with symptoms, 6 months after the discontinuation of cisplatin–etoposide. The reduction in tumor activity seen in previously highly active hilar area and left adrenal gland is indicative of the efficacy of pembrolizumab in the management of PD-L1 positive NSCLC. Unfortunately, the primary mass had progressed to its approximate size at presentation and the mixed response to immunotherapy has warranted an escalation to third line therapy with ramucirumab and docetaxel in accordance with FDA-approved guidelines for the management of treatment-resistant NSCLC. As previous case reports indicate, prognosis of HAC of the lung is poor [5], especially for non-resectable disease (Table 1). Patient's clinical course has spread over 10 months as of February 10, 2019. This also indicated a promising result for the use of immune-targeted therapy in the management of advanced HAC of the lung.

Patient is status post 3 cycles of ramucirumab. Tolerating therapy well and with negative symptomatology. Last CT shows a regression of the primary mass in the RUL and the mass in the right thoracic inlet. Time since diagnosis: 14 months.

Author Contribution A. El Khoury and M. El Khoury wrote the manuscript under guidance and direction from R. De Luca.

Compliance with ethical guidelines

Conflict of interest A. El Khoury, M. El Khoury and R. De Luca declare that they have no competing interests.

Ethical standards Written consent for the publication of this case has been obtained from the patient.

References

1. Ishikura H, et al. An AFP-producing gastric carcinoma with features of hepatic differentiation. a case report. Cancer. 1985;56(4):840–8. https://doi.org/10.1002/1097-0142(19850815)56:4.
2. Arnould L, et al. Hepatoid Adenocarcinoma of the lung: report of a case of an unusual α-Fetoprotein-producing lung tumor. Am J Surg Pathol. 1997;21(9):1113–8. https://doi.org/10.1097/00000478-199709000-00018.

3. Su JS, et al. Clinicopathological characteristics in the differential diagnosis of Hepatoid Adenocarcinoma: a literature review. World J Gastroenterol. 2013;19(3):321–7. https://doi.org/10.3748/wjg.v19.i3.321.
4. Simmet V, et al. Chemotherapy of metastatic Hepatoid Adenocarcinoma: literature review and two case reports with Cisplatin Etoposide. Oncol Lett. 2018;15(1):48–54. https://doi.org/10.3892/ol.2017.7263.
5. Grossman K, et al. Hepatoid Adenocarcinoma of the lung: review of a rare form of lung cancer. Respir Med. 2016;119:175–9. https://doi.org/10.1016/j.rmed.2016.09.003.
6. Shao Y, et al. Hepatoid Adenocarcinoma of the lung: a case report. Int J Clin Exp Pathol. 2016;9(3):4067–4072.
7. Yasunami R, et al. Primary lung cancer producing Alpha-Fetoprotein: a case report. Cancer. 1981;47(5):926–9. https://doi.org/10.1002/1097-0142(19810301)47:5.
8. Yokoyama K, et al. An autopsied case of Alpha-Fetoprotein (AFP) producing large cell carcinoma of the lung. Japanese J Thorac Surg. 1981;34(8):609–12. Author's Translation.
9. Miyake M, et al. A case report of two patients with primary lung cancer secreting AFP. J Japanese Assoc Thorac Surg. 1986;34(6):914–9.
10. Miyake M, et al. Alpha-fetoprotein and human Chorionic Gonadotropin-producing lung cancer. Cancer. 1987;59(2):227–32. https://doi.org/10.1002/1097-0142(19870115)59:2.
11. Okunaka T, et al. Primary lung cancer producing α-Fetoprotein. Ann Thorac Surg. 1992;53(1):151–2. https://doi.org/10.1016/0003-4975(92)90778-3.
12. Nasu M, et al. Hepatoid carcinoma of the lung with production of Alpha-Fetoprotein and abnormal Prothrombin: an autopsy case report. Mod Pathol. 1997;10(10):1054–8.
13. Carlinfante G, et al. Hepatoid carcinoma of the lung: a case report with Immunohistochemical, ultrastructural and in-situ hybridization findings. Histopathology. 2000;37(1):85–95. https://doi.org/10.1046/j.1365-2559.2000.00955-5.x.
14. Genova S. Hepatoid Adenocarcinoma of the lung: a case report. Internet J Pathol. 2002;2:1–5.
15. Hayashi Y, et al. Hepatoid adenocarcinoma in the lung. Cancer Treat Res. 2002;38:211–4.
16. Hiroshima K, et al. Alpha-Fetoprotein-producing lung carcinoma: report of three cases. Pathol Int. 2002;52(1):46–53. https://doi.org/10.1046/j.1440-1827.2002.01311.x.
17. Iino K, et al. A Resected case of Alpha-Fetoprotein-producing Hepatoid Adenocarcinoma of the lung. Japanese J Lung Cancer. 2003;43:29–34.
18. Oshiro Y, et al. A Resected case of Metachronous liver metastasis from lung cancer producing Alpha-Fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II). Hepatogastroenterology. 2004;51(58):1144–7.
19. Ivan M, et al. Hepatoid Adenocarcinoma of the lung. Chest. 2007;132(4):690.
20. Kishimoto T, et al. A case of α-Fetoprotein-producing pulmonary carcinoma with restricted expression of Hepatocyte nuclear factor-4α in Hepatoid foci: a case report with studies of previous cases. Hum Pathol. 2008;39(7):1115–20. https://doi.org/10.1016/j.humpath.2007.12.013.
21. Kim L, et al. Hepatoid Adenocarcinoma arising in the lung: a case report. Basic Appl Pathol. 2009;2:47.
22. Valentino F, et al. Synchronous presentation of Hepatoid Alpha-Fetoprotein-producing lung cancer and Colorectal Adenocarcinoma. Tumori. 2012;98(5):e130–e4. https://doi.org/10.1038/s41598-018-24734-z.
23. Lin S-F, et al. Primary pulmonary Hepatoid carcinoma: report of a case and review of the literature. Kao Hsiung I Hsueh Ko Hsueh Tsa Chih. 2013;29(9):512–6. https://doi.org/10.1016/j.kjms.2013.01.007.
24. Haninger DM, et al. Hepatoid Adenocarcinoma of the lung: report of five cases and review of the literature. Mod Pathol. 2014;27(4):535–42. https://doi.org/10.1038/modpathol.2013.170.
25. Shaib W, et al. Hepatoid Adenocarcinoma of the lung: a case report and review of the literature. J Gastrointest Cancer. 2014;45(1):99–102. https://doi.org/10.1007/s12029-013-9558-7.
26. Che Q-Y, et al. Hepatoid Adenocarcinoma of the lung: presenting Mediastinal metastasis without transfer to the liver. Oncol Lett. 2014;8(1):105–10. https://doi.org/10.3892/ol.2014.2064.
27. Gavrancic T, Park Y-H. A novel approach using Sorafenib in Alpha Fetoprotein-producing Hepatoid Adenocarcinoma of the lung. J Natl Compr Cancer Netw. 2015;13(4):387–91. https://doi.org/10.6004/JNCCN.2015.0054. quiz 391.
28. Qian GQ, et al. Hepatoid Adenocarcinoma of the lung. QJM. 2016;109(9):619–20. https://doi.org/10.1093/qjmed/hcw107.
29. Motooka Y, et al. Pulmonary Hepatoid Adenocarcinoma: report of a Case. Surg Case Rep. 2016;2(1):1. https://doi.org/10.1186/s40792-016-0129-6.
30. Sun JN, et al. Hepatoid Adenocarcinoma of the lung without production of α-Fetoprotein: a case report and review of the literature. Oncol Lett. 2016;12(1):189–94. https://doi.org/10.3892/ol.2016.4559.
31. Valle L, et al. Hepatoid Adenocarcinoma of the lung metastasizing to the tonsil. Mol Clin Oncol. 2017;6(5):705–7. https://doi.org/10.3892/mco.2017.1215.
32. Basse V, et al. A mismatch repair—deficient Hepatoid Adenocarcinoma of the lung responding to anti-PD-L1 Durvalumab therapy despite no PD-L1 expression. J Thorac Oncol. 2018;13(7):e120–e2. https://doi.org/10.1016/j.jtho.2018.03.004.
33. Debruyne EN, Delanghe JR. Diagnosing and monitoring Hepatocellular carcinoma with Alpha-Fetoprotein: new aspects and applications. Clin Chimica Acta. 2008;395(1–2):19–26. https://doi.org/10.1016/J.CCA.2008.05.010.