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Spontaneous regression of lung metastases in hepatocellular carcinoma: A case report

Daisuke Muroya*, Toshihiro Sato, Hisamune Sakai, Toru Hisaka, Yoshito Akagi, Koji Okuda

Department of Surgery, Kurume University, 67 Asahimachi, Kurume, Fukuoka Prefecture, 830-0003, Japan

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ABSTRACT

INTRODUCTION: Spontaneous regression of hepatocellular carcinoma (HCC) is a rare condition. However, although there have been multiple reports of spontaneous regression, the definitive pathogenic mechanism of this phenomenon is still unclear.

CASE PRESENTATION: We encountered a case of a 78-year-old man who was undergoing dialysis for end-stage kidney disease with hepatitis C virus-associated chronic hepatitis presenting with HCC. The patient had previously undergone right lobectomy of the liver, but the cancer recurred with multiple lung metastases after 5 months. Approximately 13 months after the initial diagnosis of recurrence, the lung metastases decreased in size and eventually resolved without any anticancer therapy. The patient remains alive for over 41 months after recurrence.

DISCUSSION: Based on our case and literature, Hypoxia with hypotension due to hemodialysis can reduce the blood and oxygen supply of the body, which may lead to the spontaneous regression of the metastatic tumors.

CONCLUSION: We herein reported a case of spontaneous regression of HCC undergoing dialysis.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers and the third most common cause of cancer-related death worldwide. The prognosis of patients with advanced HCC remains poor even if appropriate treatments are administered. Patients with distant metastasis usually die within 12 months [1]. Spontaneous regression of HCC is a well-established phenomenon since 1972 [2]. This is defined as a partial or complete disappearance of the tumor without receiving any specific treatment [3] and is a very rare phenomenon with an incidence of 0.4% [4]. Furthermore, spontaneous regression of distant metastasis is a far rarer event [5,6]. Although there have been multiple reports of spontaneous regression, the definitive pathogenic mechanism of this phenomenon is still unclear. We present a case of resected HCC in a patient undergoing dialysis who exhibited spontaneous regression of the postoperative multiple lung metastasis without receiving any treatment and achieved long-term survival without progression.

This case report has been reported in line with the SCARE Criteria [include citation]’ at the end of the introductory section [7].

2. Case presentation

A 78-year-old man with a history of hepatitis C and surgical resection of HCC was followed up for end-stage renal disease (ESRD) due to diabetes. The patient’s medical history included hepatic steatosis, hypertension, diabetes mellitus type 2 and ESRD. He had been prescribed metformin, pantoprazole, enalapril, felodipine, metoprolol. The patient was a non-smoker and non-drinker. At the age of 74 years, the patient was introduced to our hospital for HCC surgery (Fig. 1). His physical examination on admission was unremarkable. Liver enzymes and function tests, namely bilirubin (0.44 mg/dL), albumin (4.0 mg/dL), and International Normalized Ratio (1.06) were within the normal range, while creatinine was slightly elevated at 1.74 mg/dL. The patient underwent right lobectomy of the liver for HCC, and dialysis was initiated after surgery. At 5 months after the hepatic resection, computed tomography and chest radiography revealed multiple tumors in the lung, indicating metastatic disease (Fig. 2). At that time, serum protein induced by vitamin K absence or antagonist II (PIVKA-II) was abnormally elevated (648 mAU/mL). The serum alpha fetoprotein (AFP) level was 5.7 ng/mL. The patient did not receive any anticancer therapy because of his ESRD and the advanced stage of HCC. We subse-

* Corresponding author.

E-mail addresses: muroya_daisuke@med.kurume-u.ac.jp (D. Muroya), toshihiro_sato@med.kurume-u.ac.jp (T. Sato), hisamune_sakai@med.kurume-u.ac.jp (H. Sakai), toru_hisaka@med.kurume-u.ac.jp (T. Hisaka), yoshito_akagi@med.kurume-u.ac.jp (Y. Akagi), koji_okuda@med.kurume-u.ac.jp (K. Okuda).

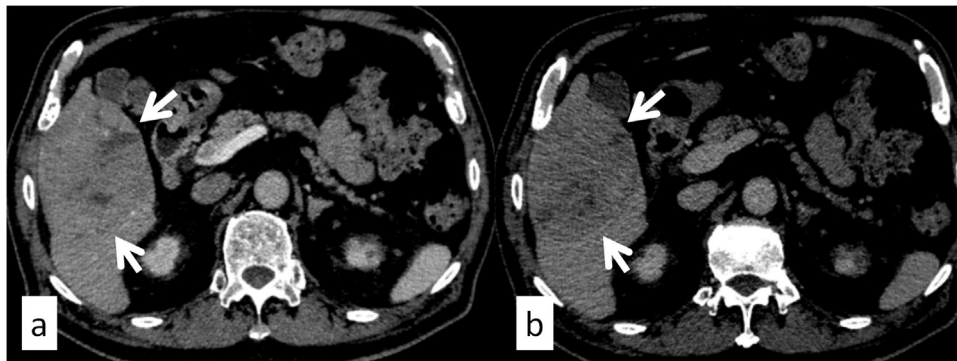


Fig. 1. Preoperative computed tomography. A mass in the right lobe of the liver measuring 9.2 × 7.2 cm (white arrow), (a) demonstrating arterial hyperenhancement and (b) washout on delayed images; findings diagnostic of hepatocellular carcinoma.

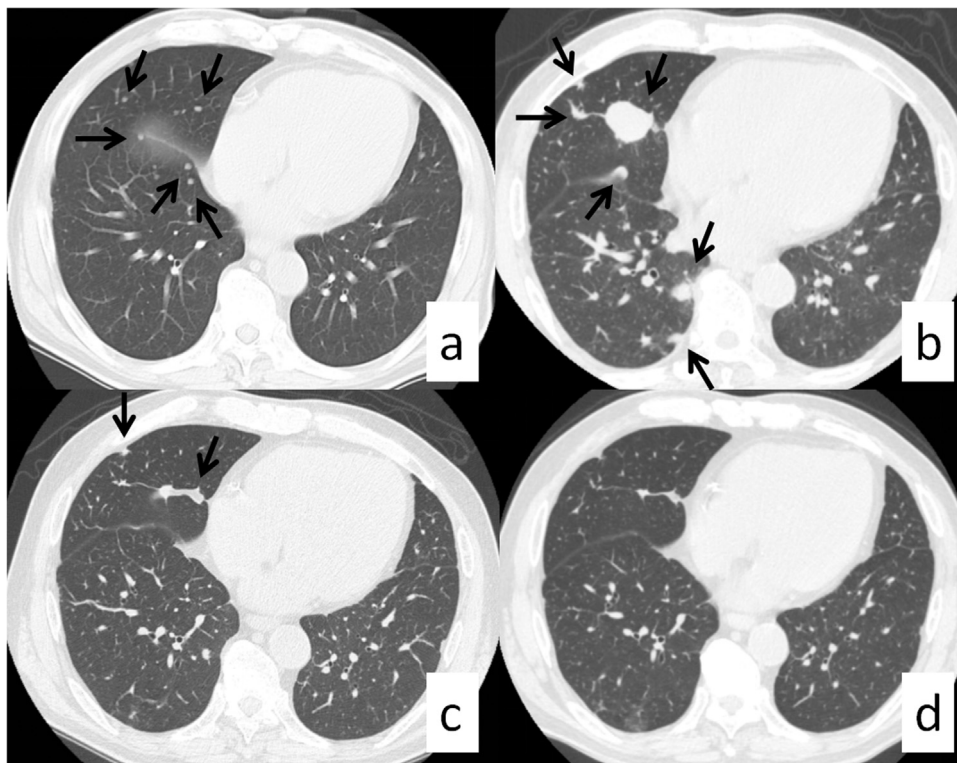


Fig. 2. (a) CT chest revealed innumerable lung nodules concerning for metastatic disease. (b) The follow-up chest CT scan revealed progression of the lung tumor 13 months after the first presentation. (c) The follow-up chest CT scan revealed spontaneous regression of the lung tumor 18 months after the first presentation. (d) Almost complete disappearance of the lung metastasis 41 months after the first presentation (arrow).

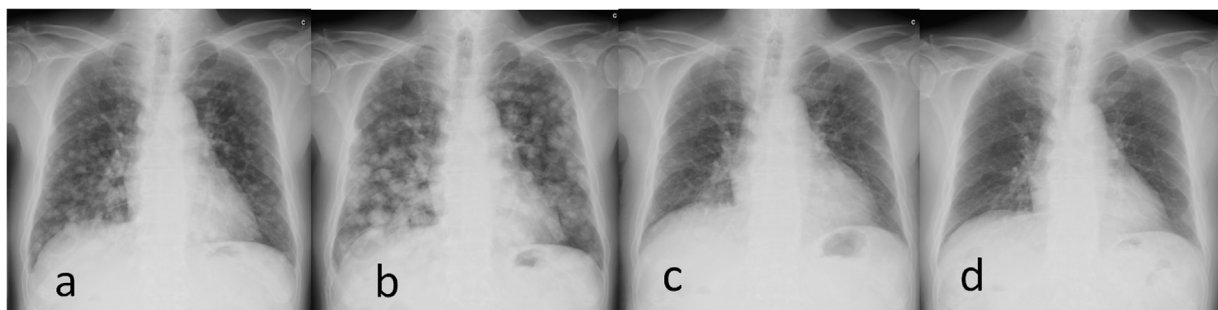


Fig. 3. (a) Chest radiography showing innumerable lung nodules indicating metastatic disease 4 months after hepatectomy. (b) The follow-up chest radiography showing progression of the lung tumor 13 months after the first presentation. (c) The follow-up chest radiography showing spontaneous regression of the lung tumor 18 months after the first presentation. (d) Almost complete disappearance of the lung metastasis 41 months after the first presentation.

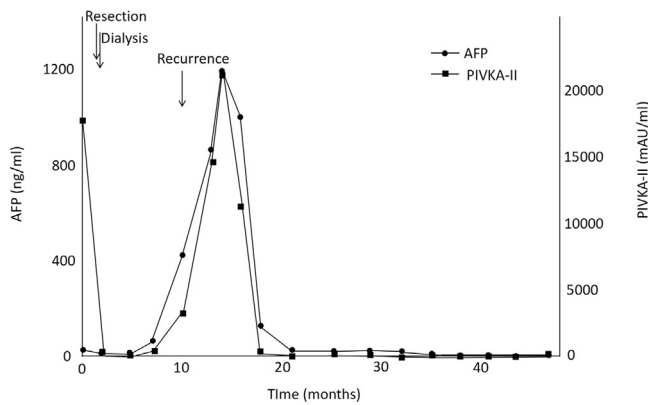


Fig. 4. Clinical course of the levels of AFP and PIVKA-II. AFP, alpha fetoprotein; PIVKA-II, protein induced by vitamin K absence/antagonist-II.

Table 1

The mechanism of spontaneous regression of hepatocellular carcinoma.

tumor hypoxia	systemic inflammatory and immunological activation
Tumor thrombosis of hepatic artery [9–11]	Abstinence from alcohol [23–25]
Tumor thrombosis of portal vein [9,10,12]	Abstinence from smoking [23]
Hepatic angiography [13]	Herbal medicine [5,26]
Tumor rapid growth [14–16]	Prolonged fever [27–29]
Hepatic arterioportal shunts [17]	Antidiabetics [30]
Massive gastrointestinal hemorrhage [18,19]	Vitamin K administration [31]
Hemodialysis [3,20]	Bacterial infection [32]
Surgical invasion [21]	Abscopal effect of radiation [33–35]
Portal vein ligation [22]	

quently followed up on his natural course with serial imaging. Chest radiography revealed an increase in the size and number of lung metastases, and tumor markers were significantly elevated 4 months after recurrence (AFP, 1198 ng/mL; PIVKA-II, 214155 mAU/mL). However, 13 months after recurrence, the metastatic lesions suddenly decreased in size and number without receiving any specific treatment or herbal medicine (Fig. 3). Follow-up imaging showed no evidence of disease progression, and tumor makers were significantly decreased (AFP, <1.0 ng/mL; PIVKA-II, 46 mAU/mL) (Fig. 4). There were no signs of new lesions on imaging or an increase in tumor markers over 41 months after the recurrence.

3. Discussion and conclusions

Spontaneous regression of cancer was first reported by Ole and Everson in 1956 [8], and the incidence rate was 1 out of 6000–10,000 cases [9]. Conventionally, this phenomenon is not uncommonly observed in malignant melanoma, neuroblastoma, and cancer of the kidney. However, in recent reports, the incidence of spontaneous regression in lung and liver cancers was also considered to be not rare. Based on the current literature review, many factors resulting in spontaneous regression of HCC have been proposed (Table 1) [9–36]. Two common mechanisms of spontaneous HCC regression were identified: tumor hypoxia and systemic inflammatory and immunological activation [31,37].

Tumor hypoxia is induced by the occlusion of the portal vein or feeding artery to the tumors, rapid tumor growth, large arterioportal shunt, chronic hypotension, and shock due to massive gastrointestinal bleeding [12,37,38]. The neoplastic tissue is more sensitive than the normal tissue to a sudden reduction in the blood and oxygen supply because of its high metabolic requirements [20].

However, our case did not have any of these pathophysiological conditions and clinical events, except for hemodialysis. Harimoto et al. [6] suggested that dialysis might play a role in the regression of HCC. In hemodialysis, there is a tendency for blood pressure to fluctuate both during and between hemodialysis treatments. Dialysis can reduce the blood and oxygen supply of the body, which may lead to the spontaneous regression of the metastatic tumors [6,39]. In the current case, the patient had started dialysis after surgery without taking any herbal medicine or consumed any new drugs. There were no symptoms suggesting a systemic inflammatory response including cholangitis, sepsis, and trauma [40,41]. The patient received no specific anticancer therapy nor had any known factors that affected tumor regression. Therefore, the spontaneous regression of HCC presented in this report may be attributed to the hypotension present during dialysis. Additionally, diabetes, the most common cause of chronic renal failure, also leads to hypotonia because of its systemic complications such as autonomic and peripheral neuropathy, macroangiopathy, and dynamic progression of atherosclerosis [42]. Although hypoxia with hypotension due to hemodialysis may be associated with the spontaneous regression of HCC, it cannot be concluded that only the dialysis affected the regression of HCC in the present case. In conclusion, we described a case of spontaneous regression of HCC undergoing dialysis. Further discussion and studies are needed to identify the mechanisms of this phenomenon, especially in association with dialysis.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Author’s contribution

Daisuke Muroya: Investigation, Writing, Supervision, Hisamune Sakai: Resources, Toru Hisaka: Resources, Yoshito Akagi: Project administration, Koji Okuda: Writing- Reviewing and Editing.

Registration of research studies

Not applicable.

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References

- [1] European association for the study of the liver, *J. Hepatol.* 56 (2012) 908–943.
- [2] F.L. Johnson, K.G. Lerner, M. Siegel, J.R. Feagler, P.W. Majerus, J.R. Hartmann, et al., Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma, *Lancet* 2 (1972) 1273–1276.
- [3] T.C. Everson, W.H. Cosle, Spontaneous regression of cancer: preliminary report, *Ann. Surg.* 144 (1956) 366–380.
- [4] S. Oquifena, F. Guillen-Grima, M. Iñarriraegui, J.M. Zozaya, B. Sangro, Spontaneous regression of hepatocellular carcinoma: a systematic review, *Eur. J. Gastroenterol. Hepatol.* 21 (2009) 254–257.
- [5] H.D. Lim, W.K. Park, I.S. Lee, Spontaneous complete regression of multiple metastases of hepatocellular carcinoma: a case report, *Oncol. Lett.* 7 (2014) 1225–1228.
- [6] N. Harimoto, K. Shirabe, K. Kajiyama, et al., Spontaneous regression of multiple pulmonary recurrences of hepatocellular carcinoma after hepatectomy: report of a case, *Surg. Today* 42 (2012) 475–478.
- [7] R.A. Agha, T. Franchi, C. Sohrabi, G. Mathew, A. Kerwan, SCARE Group, The SCARE 2020 guideline: updating consensus Surgical Case Report (SCARE) guidelines, *Int. J. Surg.* 84 (2020) 226–230, <http://dx.doi.org/10.1016/j.ijsu.2020.10.034>.
- [8] W.H. Cole, T.C. Everson, Spontaneous regression of cancer: preliminary report, *Ann. Surg.* 144 (1956) 366–383.
- [9] W.H. Cole, Efforts to explain spontaneous regression of cancer, *J. Surg. Oncol.* 17 (1981) 201–209.
- [10] E. Pectasides, R. Mikasid, S. Pyatvirat, A. Srivastava, A. Bullock, Spontaneous regression of hepatocellular carcinoma with multiple lung metastases: a case report and review of the literature, *Dig. Dis. Sci.* 61 (2016) 2749–2754, <http://dx.doi.org/10.1007/s10620-016-4141-2>, PMID: 27038447.
- [11] S. Matsuoka, A. Tamura, M. Moriyama, H. Fujikawa, K. Mimatsu, T. Oida, M. Sugitani, Pathological evidence of the cause of spontaneous regression in a case of resected hepatocellular carcinoma, *Intern. Med.* 54 (2015) 25–30, <http://dx.doi.org/10.2169/internalmedicine.54.2981>, PMID: 25742889.
- [12] S. Imaoka, Y. Sasaki, S. Masutani, O. Ishikawa, H. Furukawa, T. Kabuto, M. Kameyama, S. Ishiguro, Y. Hasegawa, H. Koyama, Necrosis of hepatocellular carcinoma caused by spontaneous arising arterial thrombus, *Hepatogastroenterology* 41 (1994) 359–362 [PMID:7525432].
- [13] T. Saito, M. Naito, Y. Matsumura, H. Kita, T. Kanno, Y. Nakada, M. Hamano, M. Chiba, K. Maeda, T. Michida, T. Ito, Spontaneous regression of a large hepatocellular carcinoma with multiple lung metastases, *Gut Liver* 8 (2014) 569–574, <http://dx.doi.org/10.5009/gnl13358>, PMID: 25228980.
- [14] K. Takayasu, Y. Muramatsu, Y. Shima, N. Moriyama, T. Yamada, T. Yoshida, M. Makuuchi, K. Kishi, Necrosis of hepatocellular carcinoma as a result of subintimal injury incurred by hepatic angiography: report of two cases, *Am. J. Gastroenterol.* 81 (1986) 979–983 [PMID: 3020974].
- [15] M.A. Alam, D. Das, Spontaneous regression of hepatocellular carcinoma—a case report, *J. Gastrointest. Cancer* 48 (2017) 194–197, <http://dx.doi.org/10.1007/s12029-016-9812-x>, PMID: 16981333.
- [16] T. Nakajima, M. Moriguchi, T. Watanabe, M. Noda, N. Fuji, M. Minami, Y. Itoh, T. Okanou, Recurrence of hepatocellular carcinoma with rapid growth after spontaneous regression, *World J. Gastroenterol.* 10 (2004) 3385–3387, <http://dx.doi.org/10.3748/wjg.v10.i22.3385>, PMID: 15484326.
- [17] M. Iwasaki, J. Furuse, M. Yoshino, N. Moriyama, H. Kanemoto, H. Okumura, Spontaneous regression of hepatocellular carcinoma: a case report, *Jpn. J. Clin. Oncol.* 27 (1997) 278–281 [PMID: 9379519].
- [18] Y. Takeda, N. Wakui, Y. Asai, N. Dan, Y. Yamauchi, N. Ueki, T. Otsuka, N. Oba, S. Nishinakagawa, M. Minagawa, Y. Takeda, S. Shiono, T. Kojima, Spontaneous complete necrosis of hepatocellular carcinoma: a case report and review of the literature, *Oncol. Lett.* 9 (2015) 1520–1526, <http://dx.doi.org/10.3892/ol.2015.2937>, PMID: 25788993.
- [19] S. Kondo, T. Okusaka, H. Ueno, M. Ikeda, C. Morizane, Spontaneous regression of hepatocellular carcinoma, *Int. J. Clin. Oncol.* 11 (2006) 407–411, <http://dx.doi.org/10.1007/s10147-006-0591-4>, PMID: 17058140.
- [20] G. Tocci, A. Conte, P. Guarascio, G. Visco, Spontaneous remission of hepatocellular carcinoma after massive gastrointestinal hemorrhage, *MBJ* 300 (1990) 641–642 [PMID: 2157513].
- [21] Y. Sato, K. Fujiwara, S. Nakagawa, S. Kanishima, Y. Ohta, Y. Oka, S. Hayashi, H. Oka, A case of spontaneous regression of hepatocellular carcinoma with bone metastasis, *Cancer* 56 (1985) 667–671 [PMID: 2408740].
- [22] H. Iijima, Y. Moriwaki, T. Yamamoto, S. Takahashi, T. Nishigami, T. Hada, Spontaneous regression of hepatic adenoma in a patient with glycogen storage disease type I after hemodialysis: ultrasonographic and CT findings, *Intern. Med.* 40 (2001) 891–895 [PMID: 11579951].
- [23] Y. Goto, Y. Uchino, S. Sasaki, N. Shirahama, Y. Nomura, J. Akiba, H. Ishikawa, Y. Akage, H. Tanaka, K. Okuda, Complete spontaneous necrosis of hepatocellular carcinoma accompanied by portal vein tumor thrombosis: a case report, *Int. J. Surg. Case Rep.* 44 (2018) 220–225, <http://dx.doi.org/10.1016/j.ijscr.2018.02.045>, PMID: 29544184.
- [24] R. Saito, H. Amano, T. Abe, N. Fujikuni, M. Nakahara, S. Yonehara, K. Teramen, T. Noriyuki, Complete spontaneous necrosis of hepatocellular carcinoma confirmed on resection: a case report, *Int. J. Surg. Case Rep.* 22 (2016) 70–74, <http://dx.doi.org/10.1016/j.ijscr.2016.03.027>, PMID: 27060644.
- [25] H.S. Lee, J.S. Lee, G.W. Woo, J.H. Yoon, C.Y. Kim, Recurrent hepatocellular carcinoma after spontaneous regression, *J. Gastroenterol.* 35 (2000) 552–556 [PMID: 10905365].
- [26] M. Grossmann, R. Hoermann, M. Weiss, K.W. Jauch, H. Oertel, A. Staebler, K. Mann, D. Engelhardt, Spontaneous regression of hepatocellular carcinoma, *Am. J. Gastroenterol.* 90 (1995) 1500–1503 [PMID: 7544955].
- [27] C. Jianxin, X. Qingxia, W. Junhui, Z. Qinrong, A case of recurrent hepatocellular carcinoma acquiring complete remission of target lesion with treatment with traditional Chinese medicine, *Integr. Cancer Ther.* (2016), <http://dx.doi.org/10.1177/1534735416660617>, Epub ahead of print [PMID: 27444311].
- [28] T. Tomino, Y. Yamashita, T. Iguchi, S. Itoh, M. Ninomiya, T. Ikegami, T. Yoshizumi, Y. Soejima, H. Kawanaka, T. Ikeda, S. Aishima, K. Shirabe, Y. Maehara, Spontaneous massive necrosis of hepatocellular carcinoma with narrowing and occlusion of the arteries and portal veins, *Case Rep. Gastroenterol.* 8 (2014) 148–155, <http://dx.doi.org/10.1159/000362440>, PMID: 24926228.
- [29] S. Markovic, V. Ferlan-Marolt, Z. Hlebanja, Spontaneous regression of hepatocellular carcinoma, *Am. J. Gastroenterol.* 91 (1996) 392–393 [PMID: 8607517].
- [30] E. Stoelben, M. Koch, S. Hanke, A. Lossnitzer, H.J. Gaertner, K.U. Schentke, A. Bunk, H.D. Saeger, Spontaneous regression of hepatocellular carcinoma confirmed by surgical specimen: report of two cases and review of the literature, *Langenvecks Arch. Surg.* 383 (1998) 447–452 [PMID: 9921945].
- [31] H. Kato, M. Nakamura, M. Muramatsu, E. Orito, R. Ueda, M. Mizokami, Spontaneous regression of hepatocellular carcinoma: two case reports and a literature review, *Hepatol. Res.* 29 (2004) 180–190, <http://dx.doi.org/10.1016/j.jhepres.2004.03.005>, PMID: 15203083.
- [32] K. Nouse, S. Uematsu, K. Shiraga, R. Okamoto, R. Harada, S. Takayama, W. Kawai, S. Kimura, T. Ueki, N. Okano, M. Nakagawa, M. Mizuno, Y. Araki, Y. Shiratori, Regression of hepatocellular carcinoma during vitamin K administration, *World J. Gastroenterol.* 11 (2005) 6722–6724, <http://dx.doi.org/10.3748/wjg.v11.i42.6722>, PMID: 16425373.
- [33] K.C. Lam, J.C. Ho, R.T. Yeung, Spontaneous regression of hepatocellular carcinoma: a case study, *Cancer* 50 (1982) 332–336.
- [34] K. Okuma, H. Yamashita, Y. Niibe, K. Hayakawa, K. Nakagawa, Abscopal effect of radiation on lung metastases of hepatocellular carcinoma: a case report, *J. Med. Case Rep.* 5 (2011) 111.
- [35] S.W. Nam, J.-Y. Han, J.I. Kim, et al., Spontaneous regression of a large hepatocellular carcinoma with skull metastasis, *J. Gastroenterol. Hepatol.* 20 (2005) 488–492.
- [36] K. Ohba, K. Omagari, T. Nakamura, et al., Abscopal regression of hepatocellular carcinoma after radiotherapy for bone metastasis, *Gut* 43 (1998) 575–577.
- [37] J.I. Huz, M. Melis, U. Sarpel, Spontaneous regression of hepatocellular carcinoma is most often associated with tumor hypoxia or a systemic inflammatory response, *HPB* 14 (2012) 500–505.
- [38] T. Iiai, Y. Sato, N. Nabatame, S. Yamamoto, S. Makino, K. Hatakeyama, Spontaneous complete regression of hepatocellular carcinoma with portal vein tumor thrombus, *Hepatogastroenterology* 50 (2003) 1628–1630.
- [39] J.A. Jensen, W.H. Goodson 3rd, R.S. Omachi, S.M. Lindenfeld, T.K. Hunt, Subcutaneous tissue oxygen tension falls during hemodialysis, *Surgery* 101 (1987), 416–412.
- [40] H. Ohta, Y. Sakamoto, H. Ojima, Y. Yamada, T. Hibi, Y. Takahashi, et al., Spontaneous regression of hepatocellular carcinoma with complete necrosis: case report, *Abdom. Imaging* 30 (2005) 734–737.
- [41] A.C. Randolph, E.M. Tharalson, N. Gilani, Spontaneous regression of hepatocellular carcinoma is possible and might have implications for future therapies, *Eur. J. Gastroenterol. Hepatol.* 20 (2008) 804–809.
- [42] M. Sato, I. Horigome, S. Chiba, et al., Autonomic insufficiency as a factor contributing to dialysis-induced hypotension, *Nephrol. Dial. Transplant.* 16 (2001) 1657–1662.

Daisuke Muroya of Munakatasuikoukaisogo hospital in Japan. Is in charge of the department of surgery. Worked as surgeon in Kurume University hospital and associated hospital for 12 years. Qualification: PhD in medicine, Kurume University, Fukuoka (2017).

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