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Case Report

Must we wait for the development of metastasis to be able to distinguish dopamine-resistant aggressive prolactinoma from prolactin-producing pituitary carcinomas? Case report and literature review

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ABSTRACT

Prolactinomas are the most prevalent type of neuroendocrine disease, accounting for approximately 40% of all pituitary adenomas. In the vast majority of cases, these are benign tumors with excellent clinical response to medical therapy with dopamine agonist agents such as bromocriptine and cabergoline. Rarely medical treatment fails to normalize prolactin levels and/or decrease the size of the tumor, posing a challenge to the clinician. Here we present a case of a 40-year-old man, who had resection of a 7.4 cm pituitary prolactinoma *via* frontal craniotomy followed by radiotherapy. He developed panhypopituitarism and was placed on chronic hormonal replacement therapy plus high dose cabergoline. Two years later he presented with recurrence of his disease and was diagnosed with an unresectable 4.9 cm pituitary adenoma showing cortical breakthrough of the sellar floor, invasion into the optic chiasm, erosion of the posterior sphenoid walls, extension into the sphenoid sinuses and posteriorly into the pons, midbrain and third ventricle, as well as complete encasement of the distal, superior cerebellar and posterior cerebral arteries. The patient underwent endoscopic tumor resection and cerebrospinal fluid (CSF) leak repair. The pathology revealed a pituitary prolactinoma with Ki-67 of up to 8% and positive p53 immunostaining. His cabergoline dose was adjusted to 0.5 mg PO daily and he was started on Sandostatin 20 mg IM monthly as well as appropriate hormonal replacement of the other deficient pituitary hormonal axes. Follow up imaging revealed stability of the lesion. The patient continues to do clinically well and actively follows with endocrinology and neurosurgery with serial brain MRIs and laboratory workup. The histological and biochemical characteristics of aggressive prolactin secreting tumors have been reported to be of minimal utility in distinguishing benign from malignant lesions. Tumors can only be diagnosed as carcinomas after they have metastasized and they can only be classified as aggressive after treatment failure or unusual growth, which creates a disadvantage for the prognosis and management of these patients. Clinicians are in need of better guidelines that can help them identify the rare cases that might warrant more aggressive clinical interventions beyond dopamine agonists such as surgery, radiation, temozolomide, somatostatin receptor agonists and others, with the hope of delaying or preventing the development of metastasis. Case reports of atypical presentations of aggressive prolactinomas such as the one here presented, can help broaden our understanding of the predictable signs of poor prognosis.

KEYWORDS: aggressive, prolactinoma, malignant, pituitary, adenoma, tumor, metastasis.

INTRODUCTION

Pituitary adenomas are not uncommon. At autopsy, approximately 12% of scans harbor a clinically inapparent pituitary adenoma [1]. Among them, prolactinomas account for approximately 40% of cases, being the most prevalent type of neuroendocrine disease [2]. In most cases, prolactinomas are benign tumors, with excellent clinical response to medical therapy. The most typical agents used for treatment are dopamine agonists, such as bromocriptine and cabergoline, which are safe and usually well tolerated. Rarely, medical treatment fails to normalize prolactin levels and/or decrease the size of the tumor. In this situation, we should rule out other differentials such as dopamine resistance or the very rare cases of prolactin-producing pituitary carcinomas [3].

We define malignant prolactinoma as one that exhibits metastatic spread within or outside the central nervous system. Standard histology and electron microscopy are not able to distinguish between carcinoma and adenoma [3] posing a real diagnostic and therapeutic challenge to the clinician. Here we present the case of a patient with an atypical aggressive prolactinoma followed by a review of the diagnosis and management of this challenging clinical entity.

CASE REPORT

A 40-year-old man with severe headache was incidentally found to have a large pituitary mass. The mass was reported to arise from the pituitary gland and measured 7.4 cm. Due to the significant size he underwent surgical resection *via* frontal craniotomy followed by radiotherapy in Peru in the year 2018. The pathology was consistent with a prolactin-secreting tumor. He developed panhypopituitarism after surgery and started chronic hormonal replacement therapy with corticosteroids, levothyroxine, testosterone, desmopressin and cabergoline.

Two years later, he established care with endocrinology *via* telemedicine in the United States, when he complained of clear rhinorrhea, secondary to a cerebrospinal fluid (CSF) leak, persistent bitemporal hemianopsia, gynecomastia, fatigue, low libido and infertility. He denied galactorrhea.

A brain MRI with and without contrast performed in November 2020 revealed a 4.9 × 3.6 × 3.3 cm sellar/suprasellar lesion demonstrating expansion and cortical breakthrough of the sellar floor. There was evidence of perineural enhancement of the prechiasmatic and intracanalicular optic nerves with crowding of the orbital apices and erosion of the posterior sphenoid walls. The lesion extended into the sphenoid sinuses and posteriorly into the pons, midbrain and third ventricle. There was also complete encasement of the distal, superior cerebellar and posterior cerebral arteries. The images were consistent with an aggressive non-resectable adenoma/carcinoma (Figures 1 and 2).

He underwent endoscopic transsphenoidal partial resection of the tumor and CSF leak repair in December 2020. The pathology report from the surgery revealed a pituitary adenoma with positive immunohistochemistry for prolactin, PIT-1, SSTR2, Synaptophysin and CK8/18.

The immunolabeling at 4% revealed a left Sphenoid Ostium with Ki-67 proliferation index and positivity of the P53 immunostain in 20% of tumor cells. The Sphenoid Sinus tumor showed Ki-67 proliferation index at 7-8%. These results were consistent with an aggressive prolactinoma.

In February 2021, the patient's Prolactin level was 31.5 ng/ml (2-18 ng/ml) while on cabergoline 0.5 mg PO 4 times a week. Dilutions were performed on the assay and results failed to reveal any evidence of Hook effect. They also revealed decreased levels of total Testosterone at 58 ng/dL (250-1100 ng/dL), Free Testosterone 8.9 pg/mL (35-155 pg/mL), FSH <0.7 mIU/mL (1.6-8 mIU/mL) and LH <0.2 mIU/mL (1.5-9.3 mIU/mL), while temporary off testosterone replacement therapy. Free T4 was 0.7 ng/dL (0.8-1.8 ng/dL) TSH 0.06 mIU/L (0.4-4.5 mIU/L), on levothyroxine 75 mcg PO daily. Morning cortisol of 3.7 mcg/dL (4-22 mcg/dL) and ACTH level of <5 pg/mL (5-50 pg/mL) on prednisone 5 mg PO daily. IGF-1 of 115 ng/mL (52-328 ng/mL) with a growth hormone of <0.1 ng/mL (<7.1 ng/mL). Serum sodium was 140 mmol/L(135-146 mmol/L) on

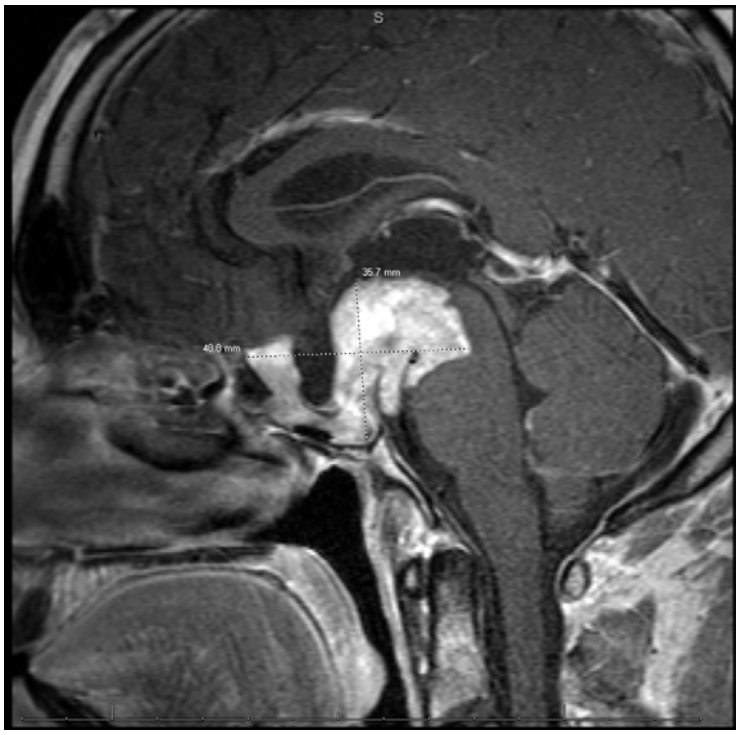

Figure 1. Brain MRI sagittal view: Aggressive non-resectable adenoma/carcinoma.

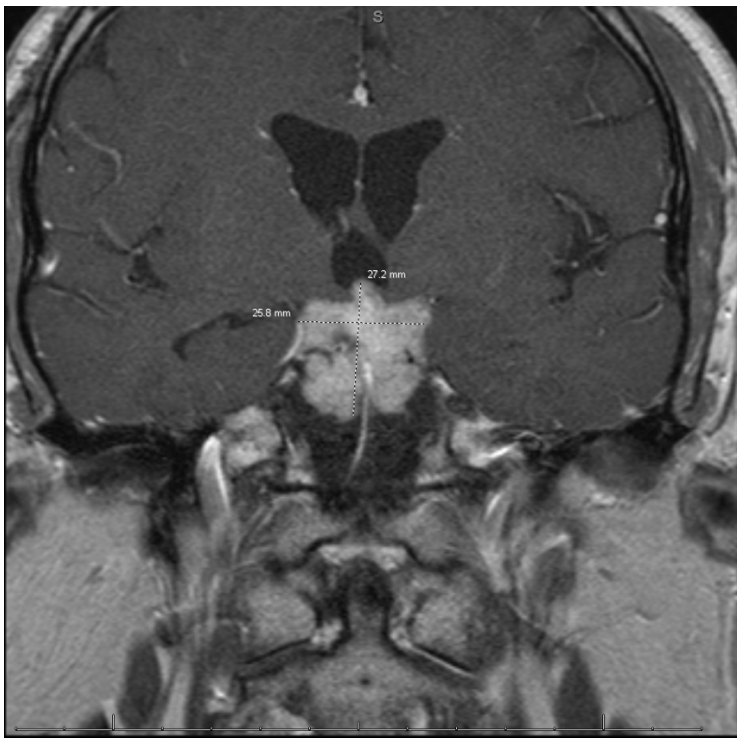

Figure 2. Brain MRI coronal view: Aggressive non-resectable adenoma/carcinoma.

treatment with desmopressin 10 mcg intranasally a day.

His medical therapy was optimized, and he started cabergoline 0.5 mg PO daily plus Sandostatin 20 mg IM monthly. Testosterone cypionate 200 mg/weekly IM injections were restarted and levothyroxine adjusted to 100 mcg PO daily. The patient reported improvement in his symptoms of fatigue and low libido.

A follow up brain MRI performed in May and November of 2021 revealed a stable lesion compared to previous. The laboratory reports from October 2021 revealed improved levels of total testosterone to 664 ng/dL, prolactin level at 30.3 ng/ml (642.36 mU/L), free T4 of 1.1 ng/dL, serum sodium of 139 mmol/L and hemoglobin A1C of 5.2%.

The patient is doing clinically well and continues to actively follow with endocrinology and neurosurgery with serial brain MRIs and laboratory workup. He is planned to start hormonal spermatogenesis induction for fertility purposes.

DISCUSSION

Prolactinomas represent the most common pituitary tumor type (47-66% of functional pituitary tumors) [4]. They are associated with hyperprolactinemia, which can result in impaired fertility, decreased libido, galactorrhea and amenorrhea [4] Tumor growth can lead to compressive mass effect resulting in headache, visual disturbances and hypopituitarism. The World Health Organization 2017 classified prolactinomas as PRL-producing adenomas and PRL-producing carcinomas. The first ones can be divided according to their size into microadenomas (<10mm), macroadenomas (equal or >10 mm) and giant prolactinomas (>40 mm). Prolactin-producing pituitary carcinomas are defined by the presence of cerebrospinal, meningeal or distant metastasis [4].

Prolactinomas are usually benign and controllable tumors because they express abundant levels of dopamine type 2 receptors (D2) [4] and usually they are successfully treated with dopaminergic drugs (bromocriptine, cabergoline). However there is a small portion of prolactinomas that does not respond to treatment; indeed they are invasive and can be clinically aggressive [4, 5].

These aggressive prolactinomas are not well-defined in the literature and some confusion exists with considerations of tumor size, tumor invasion or resistance to dopamine agonists being used as a synonym for aggressive pituitary tumor [5]. Most resistant prolactinomas are macroadenomas and resistance occurs more often in invasive tumors in men and in individuals with genetic syndromes such as MEN1 and AIP [6].

The histological and biochemical characteristics of these aggressive tumors have been reported to be of minimal utility in distinguishing benign from malignant tumors [7] because there were not true differences found. As a consequence, the European Society of Endocrinology (ESE) published some guidelines for these pituitary tumors. According to these statements a carcinoma is the tumor that metastasizes and an aggressive pituitary tumor is the tumor that is radiologically invasive with unusual rapid growth or a tumor with relevant growth despite optimal treatment (surgery, radiotherapy, conventional medical treatment). This definition underlines that in the absence of tumor progression, prolactinomas which fail to be hormonally controlled by dopamine agonist treatment should not be considered as aggressive pituitary tumors, unlike the definition of resistant prolactinoma [5]. In order to classify an aggressive prolactinomas an extended concept may embrace the biological, pathological, anatomical and clinical aspects of the tumor.

Resistant prolactinomas are defined according to the Endocrine Society as showing a failure to normalize prolactin levels or failure to obtain a significant reduction of tumor size (50% or more size reduction) on standard dose of dopamine agonist (usually considered to be up to 2 mg/week of cabergoline) [3]. The mechanisms underlying resistance are not fully understood and may be the consequence of a reduction in D2 receptor expression or alterations in the downstream signaling cascade [8].

Pituitary carcinoma defined by the presence of distant metastasis is rare (0.2% of pituitary tumors). In an ESE survey of 40 pituitary carcinomas, 15 were prolactin secreting, constituting the second most common after ACTH [9]. The prognosis of these tumors is very poor. The first

site of metastasis is usually the central nervous system, followed by lymphatic chains of the neck and systemic localization to organs such as liver, bone and lungs [10].

There are pathology markers that are taken into consideration when classifying a tumor as an aggressive prolactinoma: 2 out of 3 proliferative markers - Ki-67 index (>3% in formalin fixative), mitoses (>2/10 HPF) and positive p53 (10 strongly positive nuclei/10 HPF) [11].

PRL-secreting carcinomas' incidence is about 0.2% and their diagnosis is very challenging. Initially, malignant prolactinomas are indistinguishable histologically and clinically from aggressive adenomas and this makes the management even more difficult. These tumors can only be diagnosed as carcinomas after they have metastasized and they can only be classified as aggressive after treatment failure or unusual growth [4]. Apparently the only way we can diagnose this tumor is as we monitor their progression over time, which creates a disadvantage for the prognosis and management.

Optimal standard therapies (OST) for aggressive prolactinomas consist of: High dose cabergoline, Surgery and Radiotherapy [5]. Standard medical therapies should be optimized to ensure that continued adenoma growth is not due to under-dosing [12, 13].

Cabergoline should be administered, starting at a dose of 0.25 mg 2 times a week with up-titration as appropriate. PRL normalization has been reported with doses as high as 11 mg a week [12]. When maximal doses have been unsuccessful in controlling disease, further treatment options should be considered (maximally tolerated doses of cabergoline ranging from 10.5 to 14 mg a week) [12].

The second stage in treatment is surgical resection. MRI evidence of total adenoma removal after initial surgery correlates with long-term disease-free survival in more than 90% of patients with non-functioning adenomas (NFAs) [12]. By contrast, for patients with refractory adenomas, surgery plays a lesser role. These adenomas may invade the cavernous sinus, skull base, or intracranial structures beyond the sellar and parasellar region, reducing the opportunity for gross total resection, and there is high likelihood of further growth even with extensive resection [12]. Nonetheless, particularly for rapidly growing adenomas, reoperation can be considered to reduce mass effect in anticipation of subsequent radiation therapy (RT) or chemotherapy. In general, there is no absolute limit to the number of times transsphenoidal surgery or craniotomy can be attempted, although potential benefits are typically diminished after 3-4 surgeries [12].

RT has proven reliable when surgical resection is deemed not feasible or when medical therapy is no longer efficacious or tolerated. Treatment doses in the range of 12-15 Gy, delivered in a single fraction or in multiple fractions, can prevent further adenoma growth in more than 95% of adenomas. However, rates of radiation-induced hypopituitarism are quite significant, with at least 25% and up to 90% of patients developing a degree of anterior pituitary hormone deficiency within 10 years. A role for repeat irradiation of adenomas that progress or recur despite previous RT is far more limited due to substantial risk of radiation necrosis to adjacent brain structures, or breakdown of the carotid artery wall, leading to catastrophic bleeding or death [12, 14].

When optimal standard therapies fail, a fourth-line therapy with temozolomide [14] is the current best option [5]. It is an alkylating drug that allows control tumor growth in 50% of treated prolactinomas and improves overall survival [14]. Temozolomide may induce tumor reduction and serum prolactin reduction in 75% of cases but only 8% have a normalization of prolactin levels [14].

The specific time frame for Temozolomide introduction into the patient's regime can vary, but prompt intervention is recommended [14, 15]. 3 cycles of Temozolomide are needed in order to decide if the patient is a responder, in which case therapy is prolonged for 6 more months [4]. An efficient fifth-line therapy (or second-line treatment) after temozolomide is still lacking and re-starting the same medication usually fails to achieve a relevant clinical and imaging response [14]. Prolonged administration may be considered in certain cases on an individual multidisciplinary decision based on the patient's response to the treatment [15]. In most cases, long-term response

is limited. A need for alternative drugs persists since the majority of TU are resistant or will recur [4]. If temozolomide is inefficient or it is not tolerated by a patient with APRLs, the therapeutic options are extremely limited [14].

There are other alternative drugs such as pasireotide (a second generation somatostatin receptor ligand), that can be used in aggressive prolactinomas as an alternative therapy for non-responder tumors. They can be used before or after starting temozolomide but the literature shows effective results only in some cases and there are only a few case reports [16]. Other alternative drugs are peptide receptor radionuclide therapy (PRRT) that can be used when all other therapies have failed. These drugs can induce shrinkage and clinical improvement in ⅓ of the patients but the overall efficacy cannot be established because of the reduced data [17].

Clinicians are in need of better guidelines that can help them identify the rare cases that might warrant more aggressive clinical interventions beyond dopamine agonists such as surgery, radiation, temozolomide, somatostatin receptor agonists and others, with the hope of delaying or preventing the development of metastasis. This case presents multiple high risk features for aggressive disease that include male sex, evidence of dopaminergic-resistant hyperprolactinemia, radiologic signs of invasion and high risk histological signs (Ki-67 >3%, p53 positive). Case reports of atypical presentations of aggressive prolactinomas such as the one here presented, can help broaden our understanding of the predictable signs of poor prognosis.

CONCLUSION

The histological and biochemical characteristics of aggressive prolactin secreting tumors have been reported to be of minimal utility in distinguishing benign from malignant lesions. Tumors can only be diagnosed as carcinomas after they have metastasized and they can only be classified as aggressive after treatment failure or unusual growth, which creates a disadvantage for the prognosis and management of these patients. Clinicians are in need of better guidelines that can help them identify the rare cases that might warrant more aggressive clinical interventions beyond dopamine agonists such as surgery, radiation, temozolomide, somatostatin receptor agonists and others, with the hope of delaying or preventing the development of metastasis. Case reports of atypical presentations of aggressive prolactinomas such as the one here presented, can help broaden our understanding of the predictable signs of poor prognosis.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest.

ABBREVIATIONS

CSF	:	Cerebrospinal fluid
ESE	:	European Society of Endocrinology
OST	:	Optimal standard therapies
NFAs	:	Non-functioning adenomas
RT	:	Radiation therapy
APRLs	:	Aggressive Prolactinomas
PRRT	:	Peptide receptor radionuclide therapy

REFERENCES

1. Buurman, H. and Saeger, W. 2006, Eur. J. Endocrinol., 154(5), 753-758. doi:10.1530/eje.1.02107. PMID: 16645024.
2. Colao, A. and Savastano, S. 2011, Nat. Rev. Endocrinol., 7(5), 267-278. doi:10.1038/nrendo.2011.37. PMID: 21423245.
3. Melmed, S., Casanueva, F. F., Hoffman, A. R., Kleinberg, D. L., Montori, V. M., Schlechte, J. A. and Wass, J. A. 2011, J. Clin. Endocrinol. Metab., 96(2), 273-288. doi:10.1210/jc.2010-1692. PMID: 21296991.
4. Olarescu, N., Perez-Rivas, L., Gatto, F., Cuny, T., Tichomirowa, M., Tamagno, G. and Gahete, M. D. 2019, Neuroendocrinology, 109, 57-69. doi:10.1159/000497205.
5. Lasolle, H., Ilie, M. D. and Raverot, G. 2020, Pituitary, 23(1), 70-77. doi:10.1007/s11102-019-01000-7. PMID: 31617128.
6. Salenave, S., Ancelle, D., Bahougne, T., Raverot, G., Kamenický, P., Bouligand, J., Guiochon-Mantel, A., Linglart, A., Souchon, P. F., Nicolino, M., Young, J., Borson-Chazot, F., Delemer, B. and Chanson, P.

2015, J. Clin. Endocrinol. Metab., 100(3), 1177-1186. doi:10.1210/jc.2014-3670. PMID: 25532043.
7. Kars, M., Roelfsema, F., Romijn, J. and Pereira, A. 2006, Eur. J. Endocrinol., 155(4), 523-534. doi:10.1530/eje.1.02268.
8. Molitch, M. E. 2014, J. Neurooncol., 117(3), 421-428. doi:10.1007/s11060-013-1270-8. PMID: 24146188.
9. McCormack, A., Dekkers, O. M., Petersenn, S., Popovic, V., Trouillas, J., Raverot, G. and Burman, P. 2018, Eur. J. Endocrinol., 178(3), 265-276. doi:10.1530/EJE-17-0933. PMID: 29330228.
10. Kaltsas, G. A., Nomikos, P., Kontogeorgos, G., Buchfelder, M. and Grossman, A. B. 2005, J. Clin. Endocrinol. Metab., 90(5), 3089-3099. doi:10.1210/jc.2004-2231. PMID: 15741248.
11. Phillips, J., East, H., French, S., Melcescu, E., Hamilton, R., Nicholas, W., Fratkin, J., Parent, A., Luzardo, G. and Koch, C. 2012, Hormones (Athens), 11(4), 477-482. doi:10.14310/horm.2002.1380 PMID: 23422771.
12. Cooper, O., Bonert, V., Liu, N. and Mamelak, A. 2021, Front. Endocrinol., doi:10.3389/fendo.2021.725014.
13. Raverot, G., Burman, P., McCormack, A., Heaney, A., Petersenn, S., Popovic, V., Trouillas, J., Dekkers, O. M. and The European Society of Endocrinology. 2018, Eur. J. Endocrinol., 178(1), G1-G24. doi:10.1530/EJE-17-0796. PMID: 29046323.
14. Valea, A., Sandru, F., Petca, A., Dumitrascu, M. C., Carsote, M., Petca, R-C. and Ghemigian, A. 2021, Exper. Therap. Med., 74. doi:10.3892/etm.2021.10997.
15. Elbelt, U., Schlaffer, S. M., Buchfelder, M., Knappe, U. J., Vila, G., Micko, A., Deutschbein, T., Unger, N., Lammert, A., Topuzoglu-Müller, T., Bojunga, J., Droste, M., Johanssen, S., Kolenda, H., Ritzel, K., Buslei, R., Strasburger, C. J., Petersenn, S. and Honegger, J. 2020, J. Clin. Endocrinol. Metab., 105(3), dgz211. doi:10.1210/clinem/dgz211. PMID: 31746334.
16. Coopmans, E., van Meyel, S., Pieterman, K., Ipenburg, J., Hofland, L., Donga, E., Daly, A., Beckers, A., Lely, A. and Neggers, S. 2019, Eur. J. Endocrinol., 181(2), K21-K27. doi:10.1530/EJE-19-0279. PMID: 31167168.
17. Giuffrida, G., Ferraù, F., Laudicella, R., Cotta, O., Messina, E., Granata, F., Angileri, F., Vento, A., Alibrandi, A., Baldari, S. and Cannavò, S. 2019, Endocr. Connect., 8(5), 528-535. doi:10.1530/EC-19-0065. PMID: 30939449.