Giant Hemorrhagic Prolactinoma with Sparse Prolactin Expression Presenting with Thalamic Infarction—A Case Report

Ali GENC, MD, MSc,¹ Halil Ibrahim SUN, MD,² Burcu KASAPOGLU, PhD,³ Pinar Oz, PhD,⁴ Murat Aydın SAV, MD⁵ and Mustafa Necmettin PAMIR, MD⁶

 Consultant Neurosurgeon, Acıbadem Bodrum Hospital, Department of Neurosurgery, Mugla, Turkey; 2. Consultant Neurosurgeon, Acıbadem University, Department of Neurosurgery, Istanbul, Turkey; 3. Postdoctoral Fellow, Yeditepe University, Department of Genetics, Istanbul, Turkey; 4. Postdoctoral Fellow,
Bosphorus University, Department of Biomedical Engineering, Istanbul, Turkey; 5. Professor of Pathology, Acıbadem University, Department of Pathology, Istanbul, Turkey;
Professor of Neurosurgery, Acıbadem University, Department of Neurosurgery, Istanbul, Turkey;

Abstract

Pituitary tumors are the most common form of intracranial neoplasms. However, clinically relevant pituitary tumors presenting with disturbances of hormonal secretion or mass effect are rare and they only represent about 10 % of all surgically resected intracranial neoplasms. Prolactinomas are the most common types of pituitary adenomas. Generally, hormonal expression patterns provided by immunohistochemistry (IHC) studies are correlated with the clinical features and endocrine activity of the patients. Nonetheless, exceptions occur where the immunocytochemical staining is not concordant with the clinical picture. Pituitary adenomas presenting with apoplexy are well known. However, pituitary adenomas causing cerebral stroke and resulting in hemiplegia are unusual. Here, we report an unusual case of prolactinoma with cerebral stroke and sparse prolactin (PRL) expression. A 25-year-old woman complaining of amenorrhea, dysphasia, and left hemiplegia presented with serum PRL level in excess of 4,700 ng/ml. Pre-operational radiology images revealed a giant macroadenoma and a thalamic infarct due to carotid compression. Transcranial surgery was performed. IHC study of the adenoma revealed no hormonal expression other than sparse PRL immunoreactivity. Therefore, a sparsely granulated PRL cell adenoma was diagnosed. The patient is still under follow-up with continuing cabergoline treatment.

Keywords

Adenoma, prolactinoma, apoplexy, stroke, craniotomy

Disclosure: Ali GENC, MD, MSc, Halil Ibrahim SUN, MD, Burcu KASAPOGLU, PhD, Pinar Oz, PhD, Murat Aydın Sav, MD, and Mustafa Necmettin PAMIR, MD, have no disclosures to declare. No funding was received for the publication of this article.

Compliance with Ethics: Where applicable, all procedures were followed in accordance with the responsible committee on human experimentation and with the Helsinki Declaration of 1975 and subsequent revisions. Informed consent was received from the patient involved in this case study.

Received: September 23, 2014 Accepted: November 17, 2014 Citation: US Endocrinology, 2014;10(2):124-8 DOI: 10.17925/USE.2014.10.02.124

correspondence: Ali Genc, MD, MSc, Acıbadem Bodrum Hospital, Department of Neurosurgery, Mugla, Turkey. E: draligenc@gmail.com

Pituitary tumors are the most common form of intracranial neoplasms. Their prevalence in autopsy series was reported as 5–20 %.¹ However, clinically relevant pituitary tumors presenting with disturbances of hormonal secretion or mass effect are rare, with an estimated prevalence of 200/1,000,000 and an incidence of 2/100,000 per year.² Therefore, they only represent about 10 % of all surgically resected intracranial neoplasms.^{3,4}

Their prevalence increases with advancing age: both sexes are affected equally. They can cause a variety of endocrine syndromes and disorders¹ including panhypopituitarism, acromegaly, Cushing's disease, infertility, and visual disturbances. Recently, the diagnosis of pituitary adenomas has increased as a result of the advances in neuroimaging technologies. Due to endocrine hyperfunction, hormonally active adenomas are usually diagnosed at an earlier stage than hormonally inactive ones, which are mostly diagnosed due to the effect of local pressure exerted by the growing tumor.⁵

Based on their size, pituitary adenomas can be divided into microadenomas and macroadenomas, the latter being reserved for adenomas larger than 10 mm in diameter. On the other hand, the first histologic classification of pituitary tumors was based on tinctorial characteristics using hematoxylineosin stains on resected tissue. Tumors were accordingly classified as eosinophilic, basophilic, or chromophobic adenomas⁴ and were suggested to be associated with acromegaly, Cushing's syndrome and nonfunctioning adenomas, respectively. Later studies made such a classification irrelevant by showing that some acidophilic tumors do not produce growth hormone (GH) and some GH-producing tumors are not acidophilic. Similarly, some basophilic tumors do not cause Cushing's syndrome and more than half of the chromophobic tumors are endocrinologically active, secreting various hormones.⁴

Fortunately, with the development of immunohistochemistry (IHC), correlation of clinical features and endocrine activity became possible. IHC

studies permit a conclusive identification of the various cell types in the pituitary adenomas. Currently, the standard immunohistochemical battery includes the use of antibodies to GH, prolactin (PRL), adrenocorticotrophic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and the α -subunit of the glycoprotein hormones.⁴ Generally these hormones are expressed either singly or in various combinations. Although cellular hormonal immunoreactivity is common in pituitary tumors, there are many exceptions where the immunocytochemical staining is not concordant with the clinical or biochemical features. Classic examples are the silent corticotroph and somatotroph adenomas, in which tumor cells stain positively for ACTH and GH, respectively, and yet patients have no clinical or biochemical features of excessive hormone secretion.^{1,6-9} Silent or nonfunctioning adenomas have no clinical expression of produced hormones, either because they produce inactive molecules or do not release sufficient amount of hormones from cells to create a detectable blood level.⁴

Prolactinomas represent the majority of clinically recognized pituitary adenomas, accounting for approximately 40–45 % of all.³ However, their incidence among reported surgical series is lower because of the medical therapeutic option of these tumors.³ They are reported to occur more frequently in women than in men, particularly between the second and third decades of life, when the ratio is estimated to be 10:1. Prolactinomas vary in size at presentation with most women presenting with microadenomas, whereas men tend to have macroadenomas at diagnosis. In women, hyperprolactinemia causes oligomenorrhea or amenorrhea as well as galactorrhea. In men, however, the main presenting symptom is impotence and diminished libido, which can often be overlooked and attributed to other causes.¹

Generally, Immunohistochemical study of prolactinomas, show a high rate of PRL expression in concordance with serum PRL levels. They grow slowly with Ki-67 staining of less than 2 %.⁸ Here, we report an interesting case of pituitary adenoma with high serum levels of PRL and histologically confounding sparse PRL expression. The patient manifested a long-standing history of amenorrhea and presented with abrupt apoplectic hemiplegia due to a thalamic infarction resulting from carotid compression by the tumor.

Case Report

A 25-year-old Middle Eastern female was brought to the outpatient clinic with complaints of right-sided hemiparesis, mild right-sided facial paralysis, aphasia, and a long-standing history of amenorrhea. Her menstrual cycles became irregular 8 years ago and then completely stopped to occur. Her family reported that her hemiparesis started in her right hand 2 weeks ago and progressed into a fully blown hemiplegia within 2 days. On admission, she seemed lethargic and was only able to speak with incomprehensible words, partially able to follow commands on her left side. The visual tests were unable to be performed due to lack of adequate cooperation of the patient. Hyperactive deep tendon reflexes and diminished muscle tone were noted on her right-sided extremities.

Magnetic resonance (MR) imaging of the head showed a lobulated, encapsulated mass lesion, occupying the sella turcica, causing a notable expansion of the sella, extending into the suprasellar cistern and invading both cavernous sinuses (see *Figure 1-A*, *D*). Upward displacement of the

Figure 1: Pre-operational Radiology



Axial (A) and coronal (B) T1-weighted magnetic resonance imaging (MRI). Coronal (C) and sagittal (D) T2-weighted MRI. (E) Sagittal computer tomography (CT). (F) Axial diffusionweighted MRI. MR imaging of the head (A–D) showed a lobulated, encapsulated mass lesion, occupying the sella turcica, causing a notable expansion of the sella, extending into the suprasellar cistern and invading both cavernous sinuses. A large ischemic area with hypointensity on T1-weighted images (A, B) and hyperintensity on both T2- (C, D) and diffusion-weighted (F) images could be observed. Cranial CT (E) revealed a spherical dilation and thinning of the sellar wall in all directions.

Table 1: Pre-operational and Post-operational Blood Test Results

Blood Test	Pre-operational Value (Unit)	Post-operational value (Unit)
Prolactin	>4700 ng/ml	605 ng/ml
IGF-1	332.5 ng/ml	
Cortisol	1.09 µg/dl	1.67 µg/dl
ACTH	<1 pg/ml	
FSH	0.718 ml/U/ml	
LH	<0.1 ml/U/ml	
TSH	0.3 µlU/ml	0.159 µl/U/ml
FT3	3.0 pmol/ml	1.1 pmol/l
FT4	6.0 pmol/ml	5.68 pmol/l

ACTH = adrenocorticotrophic hormone; FSH = follicle-stimulating hormone; FT3 = free triiodothyronine; FT4 = free thyroxine; IGF = insulin-like growth factor; TSH = thyroid-stimulating hormone.

Figure 2: Early Post-operative Magnetic Resonance Imaging



T1-weighted axial (left), coronal (middle) and sagittal (right) magnetic resonance imaging reveals a small residual tumor.

optic chiasm and hypothalamus was noted. Also, the left carotid syphon seemed to have a remarkably diminished caliber compared with the right.

Figure 3: Histopathology



Original magnification factors and staining techniques are given in parenthesis. A. Pituitary adenoma with extensive hemorrhagic foci were displayed (hematoxylin-eosin [H&E] staining, x100). B. Monotonous adenoma cells displayed hyperchromatic nuclei wrapped by acidophilic cytoplasm with intervening extravasated erythrocytes (H&E staining, x200). C. Adenoma cells exhibited scarce prolactin [PRL] immunoreactivity (immunohistochemistry [HC] with streptavidin biotinylated complex [SBC] and PRL antibody, x400). D. Adenoma was shown to lack reticulum framework, which is assumed to be a striking feature of pituitary neoplasms (silver impregnating staining, x40). E. Adenoma cells exhibited a low Ki67 labeling index of <1 % (IHC with SBC and Ki67 antibody, x400).

The sellar lesion showed a cystic expansion to the right and superior aspect, while revealing a solid component with mottled enhancement on the left after gadolinium injection. Left carotid syphon was noted to be under compression due to a pronounced invasion of the left cavernous sinus by the lesion. Also, a large ischemic area with hypointensity on T1-weighted images (see Figure 1-A, B) and hyperintensity on both T2-(see Figure 1-C, D) and diffusion-weighted (see Figure 1-F) images was noted. Commensurate with the patient's hemiparesis, the ischemic region involved the left thalamic structures and the left internal capsule as well as subcortical sections of the pyramidal tract. Slight contrast enhancement and hypointense impression on ADC map of the ischemic lesion was in agreement with a subacute infarction coinciding with the history of stroke happening 2 weeks earlier. A cranial computed tomography (CT) was ordered to investigate for bony erosion, which revealed a spherical dilation and thinning of the sellar wall in all directions (see Figure 1-E). No signs of complete erosion or cerebrospinal fluid (CSF) fistula were found. Pituitary adenoma, craniopharyngioma, and meningioma were considered among differential diagnoses. Cardiac workup including an echocardiography was performed to rule out any possible cardiogenic etiology of thromboembolism, which returned normal results.

Complete blood count (CBC) and biochemical workup revealed normal results including normal electrolytes. Blood tests results for pre-op levels of PRL, insulin-like growth factor 1 (IGF-1), ACTH, cortisol, FSH, and LH are given in Table 1. All pituitary hormonal axes were undisturbed except for PRL and ACTH. Prolactin level was measured at 4,700 ng/ml. The patient was considered to have a prolactinoma. Immediate surgical treatment was planned and a left pterional craniotomy was performed. Sylvian dissection was used to expose the suprasellar mass. The tumor cyst was easily accessible through optico-carotid angle due to sellar expansion. Left carotid artery seemed pale due to tumor compression. A soft, pink-to-purple cyst wall was noted. The cyst was incised and internal decompression was obtained. The cyst was filled with a necrotic yellow-colored paste, which was attributed to the apoplectic bleeding thought to occur 2 weeks earlier. Pink-to-purple chunks of tumor tissue were evacuated from the bottom of the encapsulating cyst, by using pituitary ring curettes. Intraoperative frozen section study of these chunks strongly indicated a pituitary adenoma. The remaining cystic wall was dissected away from both optic nerves and the right carotid artery. Normal pituitary gland and a thinned stalk were noted on the right side of the sella adherent to tumor capsule. However, the capsule was strictly adhered to the left carotid artery and the bottom of the sella. Therefore, the adhered capsule was left in place in order to avoid carotid injury. Following closure, the patient was not extubated and moved to an intensive care unit (ICU) under continuing sedation in order to prevent cerebral revascularization injury. She was extubated the next day and immediate improvement in her hemiparesis was noted. Postop MRI revealed a residual tumor in the left cavernous sinus (see Figure 2). Prolactin level was decreased to 605 ng/ml on postop day 1 and she was immediately started on cabergoline. Also, hypothyroidism and hypocortisolemia were noted, which were replaced by levothyroxine and methylprednisolone, respectively. She also developed a transient diabetes insipidus, which spontaneously resolved within 4 days. She was moved out of ICU on postop day 2 and started on physiotherapy sessions.

Histologic examination of the tumor under light microscopy revealed an acidophilic adenoma (see *Figure 3-B*) with hyperchromatic eccentric nuclei surrounded by polygonal, abundant cytoplasm. In addition to widespread minute hemorrhages (see Figure 3-A), apoptotic bodies were extensively scattered in tumor tissue, which were attributed to the apoplectic bleeding. No evidence of multinucleate cells or mitotic figures was present. Adenoma tissue was lacking a reticulin framework with silver impregnation stain (see Figure 3-D). Immunohistochemical battery of pituitary endocrine markers, including GH, ACTH, LH/FSH, and TSH were all negative and surprisingly, there was only a scarce PRL immunoreactivity that was less than 20 % (see Figure 3-C). Methylated O6-methylguanine-DNA methyltransferase (MGMT) reactivity was 10-20 %. Nuclear p53 oncoprotein reactivity was negative. A low Ki67 LI of <1 % was calculated (see Figure 3-E). No immunoreactivity for pancytokeratin was present. These immunohistopathologic features were consistent with a sparsely granulated PRL cell adenoma undergoing an extensive pituitary apoplexy. Therefore, the final diagnosis of sparsely granulated PRL cell adenoma was reported despite very high serum PRL levels.

After the patient was released, cabergoline treatment was continued. Blood PRL levels were monitored regularly and the values at both month 4 and 7 were 50 ng/ml. MR imaging at 7 months after the operation indicated complete stability (see *Figure 4*). She reported a complete recovery of her motor functions.

Discussion

Prolactinomas are slow-growing tumors and constitute the main group of patients with pituitary adenoma. They present with serum PRL levels exceeding 200 ng/ml and histologically show strong PRL immunoreactivity. However, the histologic examination of the adenoma in our case revealed sparse PRL immunoreactivity despite exceedingly high PRL secretion with a serum level at 4,700 ng/ml. Prolactinomas, typically, show a good correlation between tumor volume and serum PRL level with 100 % PRL immunoreactivity of tumor cells. However, pituitary adenomas are known to present with hormone expression patterns incongruous with detectable serum hormone levels. Ogawa et al. reported on a case of null cell adenoma with weak somatostatin expression and low serum hormone levels.9 Nonetheless, we could not find any reports of prolactinomas with sparse PRL expression associated with extreme serum PRL levels. Kovacs et al. proposed that either fully or scarcely, PRL immunoreactive cases might express a specific ultrastructural pattern consistent with lactotropes, such as a rough-surfaced endoplasmic reticulum with Nebenkern formation, prominence of Golgi apparatus, presence of misplaced exocytosis, as well as pleomorphism of secretory granules with a considerable variation of size ranging from 130 to 500 nm in diameter.¹⁰ They also suggested that periadenomatous lactotropes might be oversecreting PRL in a null cell adenoma, which might have been given rise to hyperprolactinemia.¹⁰

In our case, the patient was diagnosed with prolactinoma considering the combined results from MR and CT imaging and high serum PRL levels. While the radiologic tests revealed the size, structure, and location of the tumor, the blood tests confirmed the differential diagnosis as a prolactinoma. Astoundingly, the immunohistopathologic features revealed a few cells with PRL immunoreactivity and no other hormone expression. Therefore, the patient was considered to have a sparsely granulated PRL cell adenoma. For PRL-secreting pituitary adenomas (or prolactinomas), the size of the tumor usually determines the magnitude of the PRL secretion.^{11,12} For instance, PRL serum levels higher than 200 ng/ml is often accepted as the specific cut-off

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Figure 4: Radiology at Month 7 of Follow-up



Axial (left), coronal (middle), and sagittal (right) T1-weighted magnetic resonance imaging results of the patient at month 7 of postoperational follow-up indicate complete stability.

value for prolactinoma, whereas this value is usually less than 100 ng/ml for the stalk effect caused by other types of parasellar tumors by preventing inhibitory control of dopamine secreted from hypothalamus.⁹

An extreme increase in serum PRL concentrations suggests a prolactinoma. However, with giant prolactinomas, as in our case, radioimmunoassay measurements of serum PRL concentrations might result in falsely low values because of the 'hook' effect phenomenon.¹³ The initial serum PRL levels in such cases may be only mildly increased (50–150 g/l). However, the actual concentrations are often measured to be in range of several thousands by the serial dilution method. Therefore, in patients with giant tumors (>3 cm), if the initial serum PRL concentration is moderate, serial dilutions must be performed. This process is clinically important to differentiate patients with prolactinomas from others.¹

Treatment of apoplectic pituitary tumors is generally surgical intervention. The apoplectic bleeding in our patient resulted in a devastating loss of neurologic functions. Therefore, immediate surgical treatment was performed. However, dopamine agonist therapy is the primary treatment for most prolactin-secreting adenomas, even in patients with suprasellar extension and chiasmal compression.8,11 This treatment effectively normalizes the serum PRL concentration in approximately 85 % and shrinks the size of the tumor in approximately 70 % of the patients. Regular followups and careful monitoring of the patients are critical to ensure tumor regression in response to medical therapy.¹ In cases resistant to medical treatment, surgical removal via transsphenoidal or transcranial routes can be considered in the first 3 or 4 months.14 Surgical approach depends to a large degree on tumor size, its extent, the patient's preference, and the available expertise for the managing surgeon. It should be noted that tumor extensions beyond the sella decreases the success probability of the surgery to less than 50 %.14 However, experienced surgeons may achieve complete or near-complete adenomectomy, with normalization of serum PRL concentration in 60-70 % of the patients. In 20-50 % of these patients, recurrences may occur over a 10-year period.^{11–14}

Another option for treatment of adenomas is radiotherapy. Traditional radiotherapy is largely being replaced by gamma knife radiosurgery lately due to its increasing availability. Gamma knife treatment is reserved for patients with microadenomas resistant to medical treatment or with residual tumors following surgery.¹⁵

Although it is well known that the brain tumors may cause stroke, pituitary adenoma accompanied with ischemia and stroke is rare.^{16–18} In our case, MRI findings showed that the reason for the patient's hemiplegia was the ischemia in the left thalamic structures and internal capsule as well as subcortical sections of the pyramidal tract. Most of the symptomatic obstructions of internal carotid arteries in pituitary adenoma patients are reported to result from pituitary apoplexies. Pituitary apoplexy, a severe yet uncommon complication of pituitary adenomas, is characterized as enlargement of the tumor due to sudden hemorrhage or ischemia.¹⁶ In our case, carotid compression was noted intraoperatively by the pale coloration in respect to the opposite side. The most likely explanation of a

stroke in pituitary apoplexies is the extraluminal compression of the main brain vessels caused by the acute growth of the tumor. Elevated intrasellar pressure in the first weeks of pituitary apoplexy might lead to vessel occlusion.¹⁹ Especially in giant tumors, the development of collateral vessels indicates chronically compromised blood flow.¹⁷ Also, the use of dopaminergic agonists has been suggested to pose an increased risk for pituitary apoplexy.¹⁶ In most cases, a CT scan is adequate to demonstrate a pituitary apoplexy, which mandates surgical removal of the tumor. Early surgical decompression restores the blood flow and facilitates recovery of neurologic symptoms. In our case, hemiplegia was improved immediately after surgical removal of the tumor.

- Arafah BM, Nasrallah MP, Pituitary tumors: pathophysiology, clinical manifestations and management, *Endocr Relat Cancer*, 2001;8:287–305.
- Yamaguchi-Okada M, Inoshita N, Nishioka H, et al., Clinicopathological analysis of nonfunctioning pituitary adenomas in patients younger than 25 years of age, *J Neurosurg Pediatrics*, 2012;9:511–6.
- Buurman H, Saeger W, Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data, *Eur J Endocrinol*, 2006;154:753–8.
- Balinisteanu B, Ceausu RA, Cimpean AM, et al., Conventional examination versus immunohistochemistry in the prediction of hormone profile of pituitary adenomas, An analysis on 142 cases. Rom J Morohol Embryol. 2011;2(Supol. 3):1041–5.
- Saeger W, Ludecke DK, Buchfelder M, et al., Pathohistological classification of pituitary tumors: 10 years of experience with the German Pituitary Tumor Registry, *Eur J Endocrinol*, 2007;156:203–16.
- Sav A, Syro LV, Scheithauer BW, et al., Silent Somatotroph Adenoma: A Morphologic, Immunohistochemical and Electron Microscopic Study: A Case Report, J Med Cases, 2012;3(1):43–8.
- 7. Wade AN, Baccon J, Grady JKD, et al., Clinically silent

somatotroph adenomas are common, Eur J Endocrinol, 2011;165:39–44.

- Sav A, Rotondo F, Syro LV, et al., Biomarkers of pituitary neoplasms, Anticancer Res, 2012;32:4639–54.
- Ogawa Y, Watanabe M, Tominaga T, Somaostatin-producing atypical null cell adenoma manifesting as svere hypopitularism and rapid deterioration – case report, *Endocr Pathol*, 2010;21:130–4.
- Kovacs K, Horvath E, Corenblum B, et al., Pituitary chromophobe adenomas consisting of prolactin cells: a histologic, immunocytological and electron microscopic study, Virchows Arch A Pathol Anat Histol, 1975; 366:113–23.
- Maiter D, Delgrange E, Therapy of endocrine disease: the challenges in managing giant prolactinomas, *Eur J Endocrinol*, 2014;170:213–27.
- 12. Delgrange E, Raverot G, Bex M, et al., Giant prolactinomas in women, *Eur J Endocrinol*, 2014;170:31–8.
- Vilar L, Fleseriu M, Bronstein MD, Challenges and pitfalls in the diagnosis of hyperprolactinemia, Arq Bras Endocrinol Metabol, 2014;58:9–22.
- 14. Feigenbaum SL, Downey DE, Wilson CB, Jaffe RB, Transsphenoidal pituitary resection for preoperative diagnosis

of prolactin-secreting pituitary adenoma in women: long term follow-up, *J Clin Endocrinol Metab*, 1996;81:1711–9.

- Kim W, Clelland C, Yang J, Pouratian N, Comprehensive review of stereotactic radiosurgery for medically and surgically refractory pituitary adenomas, *Surg Neurol Int*, 2012;3 (Suppl. 2):S79–89.
- Möller-Goede DL, Brändle M, Landau K, et al., Pituitary apoplexy: re-evaluaion of risk factors for bleeding into pituitary adenomas and impact on outcome, *Eur J Endocrinol*, 2011;164:37–43.
- Navarro-Bonnet J, Martinez-Anda JJ, Balderrama-Soto A, et al., Stroke associated with pituitary apoplexy in a giant prolactinoma: A case report, *Clin Neurol Neurosurg*, 2014;116:101–3.
- Rey Dios R, Payner TD, Cohen-Gadol AA, Pituitary macroadenoma causing symptomatic internal carotid artery compression: Surgical reatment through transsphenoidal tumor resection, J Clin Neurosci, 2014;21:541–6.
- Zayour DH, Selman WR, Arafah BM, Extreme elevation of intrasellar pressure in patients with pituitary tumor apoplexy: relation to pituitary function, J Clin Endocrinol Metab, 2004;89:5649–54.