CASE REPORT

Pituitary carcinoma: Report of an exceptional case and review of the literature

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ABSTRACT. Pituitary carcinomas are exceptional tumors and constitute 0.1 to 0.2% of pituitary tumors. Their definition includes well-established criteria but distant metastasis is the hallmark required for diagnosis. We report the fourth case of gonadotropic pituitary carcinoma described in the literature. This case illustrates the dramatic outcome of these tumors. The most interesting feature of our case was the loss of differentiation with time, established by retrospective analysis of the primary tumor surgically treated 15 years earlier. Most of the previously reported cases exhibited a majority of adrenocoticotropin and non-functioning pituitary tumors. However, the frequency of non-functioning tumors seems smaller than previously believed. In the discussion, we stress the need to detect these very aggressive tumors as early as possible and identify treatments to improve the dramatic course of these carcinomas.

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INTRODUCTION

Pituitary adenomas are benign tumors, which either grow slowly or remain confined to the *sella turcica*. However, many of them behave like invasive tumors by growing into surrounding tissues (1, 2). Furthermore, they can display histological abnormalities such as mitotic figures (2). However, these tumors do not behave like usual malignant neoplasias, which are characterized by infiltration of both vessel walls and nerves. Nevertheless, confusion remains between very aggressive and invasive pituitary adenoma *vs* pituitary carcinoma, whose definition requires accurate definition criteria. Primary pituitary carcinomas are extremely rare tumors and constitute 0.1 to 0.2% of all pituitary tumors (3). Their definition has been a subject of debate for 60 years. Distant metastases are now generally accepted as the true diagnostic hallmark of pituitary carcinoma (3-5). Note that histological criteria for the determination of malignancy in pituitary tumors are indeed not adequate (2, 4, 6). Diagnosis of primary pituitary carcinoma is based on the following criteria: (4, 6).

- the primary tumor must be identified as a pituitary tumor by histology;
- an alternative primary tumor has to be excluded;
- the metastases must be clearly disconnected from the primary tumor;
- the structural features or marker expressions of the metastases should correspond or be similar to those of the pituitary tumor.

Until now, almost all cases of pituitary carcinoma have been primarily diagnosed in patients displaying primary adenomas, with the following proportions: 33% adrenocorticotropin adenomas, 28% prolactinomas, 23% non-secreting adenomas, and 12% somatotropic adenomas. The remaining 4% consist of 3% gonadotropic adenomas and 1% thyrotropin adenomas. We describe here the case of a patient with gonadotropic pituitary tumor, which finally fulfilled all criteria for pituitary carcinoma. The dramatic course of the disease in our patient underlines the need for energetic management.

Key-words: Pituitary, gonadotropic, carcinoma, immunochemistry, surgery, radiotherapy.

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CASE REPORT

In 1983, the patient, a 50-year-old Caucasian woman, developed a right temporal hemianopsia. Computed tomography (CT) scan of the pituitary revealed a large sellar mass with suprasellar extension. The mass was compressing the optic chiasma and revealed a peritumoral ring after contrast injection. At presentation endocrinological evaluation comprising measurement of PRL, 08:00 h plasma cortisol, serum LH and FSH, serum free T_4 and TSH revealed no abnormalities (Table 1). The pituitary tumor was resected by transfrontal craniotomy. The surgical report mentioned the hard rough nature of the tumor, making resection impossible around the right optic nerve area. The conclusion of the pathological analysis indicated the presence of a chromophobic adenoma. At that time immunocytochemistry was not performed. After surgery, ocular and pituitary functions were normal. Forty-eight Gy of radiotherapy completed incomplete surgical resection. The follow-up consisted of yearly pituitary CT scan and endocrinological check-up. In 1992, a colon carcinoma was diagnosed. It was treated by surgery and chemotherapy. The last endoscopy in 1998 was normal. In 1997, central hypothyroidism and hypogonadism were detected. At that time, cerebral and pituitary CT scans were normal. (Fig. 1 and 2). At the end of 1998, fifteen years after the first pituitary surgery, the patient complained of a sudden hemianopsia, with reduced visual acuity and headaches. Cerebral magnetic resonance imaging (MRI) demonstrated the presence of two separate tumors. One was a suprasellar tumor measuring 14 mm in diameter, compressing the optic chiasma, with extension to the third ventricle. The other one was a 15-mm diameter right frontal mass, compressing the right frontal horn of the right ventricle. After iv injection of gadolinium GdDTPA, contrast enhancement was homogeneous on T1 weighted images with a contrast enhanced peritumoral ring around the suprasellar tumor. The two tumors were completely distinct but their signal characteristics were similar. Both tumors were surgically removed in March 1999. Macroscopically, the suprasellar tumor looked like adenoma tissue, and the right frontal tumor was not suggestive of any specific lesion. Histological analysis showed similar features in the two tumors, composed of chromophobic cells with nuclear aberrations and numerous mitoses. Cytoplasmic staining for chromogranin A (a cytological marker for neuroendocrine tumors) led to the definitive diagnosis of pituitary carcinoma. Such positive staining occurred in both tumors. Immunocytochemical analysis showed absence of pituitary hormonal reactivity (Fig. 3). Histological examination completely excluded the diagnosis of colon adenocarcinoma metastases and radiation induced-tumors. Besides, we retrieved colon tumor slides; chromogranine A immunostaining was negative for the tumor and positive for neuroendocrine cells (APUD cells) localized in the normal adjacent tissue (normal control). These results excluded the

Table 1 - Endocrinological evolution.

	First pituitary surgery		Second surgery 03/18/99			
	1983 pre-surgery	1983 post-surgery	1999 pre-surgery	1999 (March) post-surgery	1999 (June)	1999 (October)
Cortisol (ng/dl)	27	24	18.1	2	2	<1
Cortisol/synacten	ND	33.5	ND	8	11	ND
ACTH (pg/ml)	ND	ND	ND	<2	<2	<2
E2 (pg/ml)	ND	ND	ND	11	<10	ND
FSH/LHRH* (mUI/ml)	26	ND	0.6	1/2.1	1.4/3.5	ND
LH/LHRH	5.4	6.7/22	<0.5	1/1	1/1	ND
FSH/TRH**	ND	29/51	ND	2.9/3.6	ND	ND
α-subunit/TRH				0.14/0.16		
α-subunit/TRH				0.14/0.15		
FT_4 (pmol/l)		15.5	11.6	14.2	13.8	17.5
TSHus/TRH		2/8	0.59	0.074		
IgF1 (ng/ml) (no.: 123-463)			<35	140		

ND: not done; *(100 µg); **(250 µg); FT_4: free T_4.

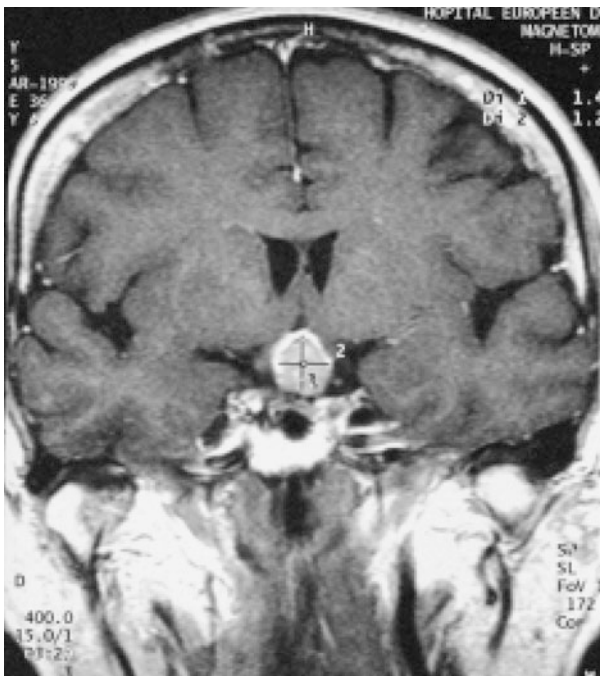

Fig. 1 - *Magnetic resonance imaging scan of the brain. Coronal T1 weighted with gadolinium. Suprasellar tumor of 14 mm diameter. Note the contrast enhanced peritumoral ring (primary pituitary malignant tumor).*

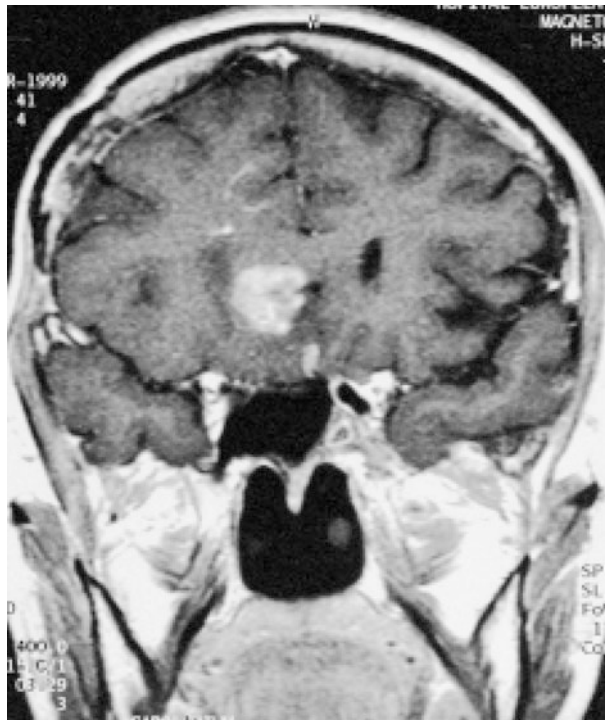

Fig. 2 - *Magnetic resonance imaging scan of the brain. Coronal T1 weighted with gadolinium. Right frontal mass (metastasis).*

possibility that the patient was presenting a neuroendocrine form of colon tumor. Concerning the pituitary adenoma, further interpretation was connected to the previous 1983 resection specimen. Retrospective pathological analysis confirmed the previous diagnosis of pituitary adenoma. However, the pathologist mentioned a rich unusual vascularisation, a regular cordonal arrangement and a slight nucleocytoplasmic atypia. Pituitary adenoma diagnosis was confirmed by positive chromogranine A staining. Furthermore, immunocytochemistry was 50% positive for FSHβ concluding many years later to a gonadotropic adenoma. Lastly, MIB1 (proliferation marker) immunostaining was negative. Postoperatively, the patient completed panhypopituitarism with a central diabetes insipidus. The hemianopsia did not regress, but the visual acuity improved. We did not find any other metastases neither systemic (abdominal and chest CT scans) nor involving the central nervous system (spinal cord MRI was normal). Our case is classified as gonadotropic cerebrospinal pituitary carcinoma. Adjuvant therapy consisted in 45 Gy of new irradiation given 5 days per week in daily fraction of 1.8 Gy and was achieved at the end of June 1999. Cerebral MRI realized respectively in April and June 1999 showed stability of the remaining frontal and pituitary lesions. In October 1999, 8 months after surgery and 3 months after the end of radiotherapy a sudden worsening occurred. Cerebral MRI revealed more than seven cerebral metastases disseminated in all the brain (4/10/99). She declined any treatment and died two months later.

DISCUSSION

Clinical presentation and tumor spread

More than one hundred pituitary carcinomas (37 ACTH, 32 PRL, 26 NS, 13 GH, 3 FSH/LH and 1 TSH) have been described in the literature until now but some of them did not fulfill all of the diagnosis criteria (4). This was due to several reasons. Firstly, confusion about previous definition criteria led to descriptions of invasive adenoma as "carcinoma" although these cases did not exhibit metastases (6). Secondly, the older cases, described at the beginning of the last century (1904) did not benefit from modern means for diagnosis such as immunohistochemistry. Thirty-two cases have been described in the last five years. All of them fulfilled the definition-criteria (1, 2, 5, 7-28). At presentation the most frequent non-endocrine complaints were visual dis-

turbance and headaches (29). Almost all cases of pituitary carcinomas arose after diagnosis and treatment (surgery and radiation therapy) of a macroadenoma several years earlier (6, 20, 29). In the review by Lubke *et al.* (6) only three cases (3/70) were referred without prior surgery or irradiation. The time period between the first manifestation of the disease and pituitary carcinoma was variable and could last from a few months to 34 years (5). All pituitary carcinomas showed a greater tendency towards craniospinal metastases (58%) than systemic metastases (35%). The remaining 7% concerned both localizations (4, 29). In general, craniospinal metastases were due to subarachnoid spread, by exposition to the cerebrospinal fluid whereas invasion of cavernous sinus allowed predisposition for venous spread and systemic diffusion (5, 6, 20). The most frequent intracranial sites of metastases were frontal and occipital lobes (30). The main metastases localization outside the brain was the liver (29). The other sites were lymph nodes, lung, and bone. Metastases rarely occurred in the heart, mediastinum or kidney (6, 8, 20, 29). Elsewhere, prolactinoma used to metastasize to the brain, and ACTH tumors outside, particularly to liver (7).

Hormonal profile, outcome and therapy options

Concerning hormonal profile, from 1904 to 1995 about 70% of pituitary carcinomas were hormone functional (29). It is important to define "functional" as including hormonal immunochemistry use and not only hormonal plasmatic measurements, particularly for gonadotropic tumors described in 1995, 1995, and 2000 respectively. Since 1995 functionality increased to 93%. Otherwise, the distribution-pattern seemed different between benign and malignant pituitary tumors (20). Indeed, the most common type of tumors found among pituitary carci-

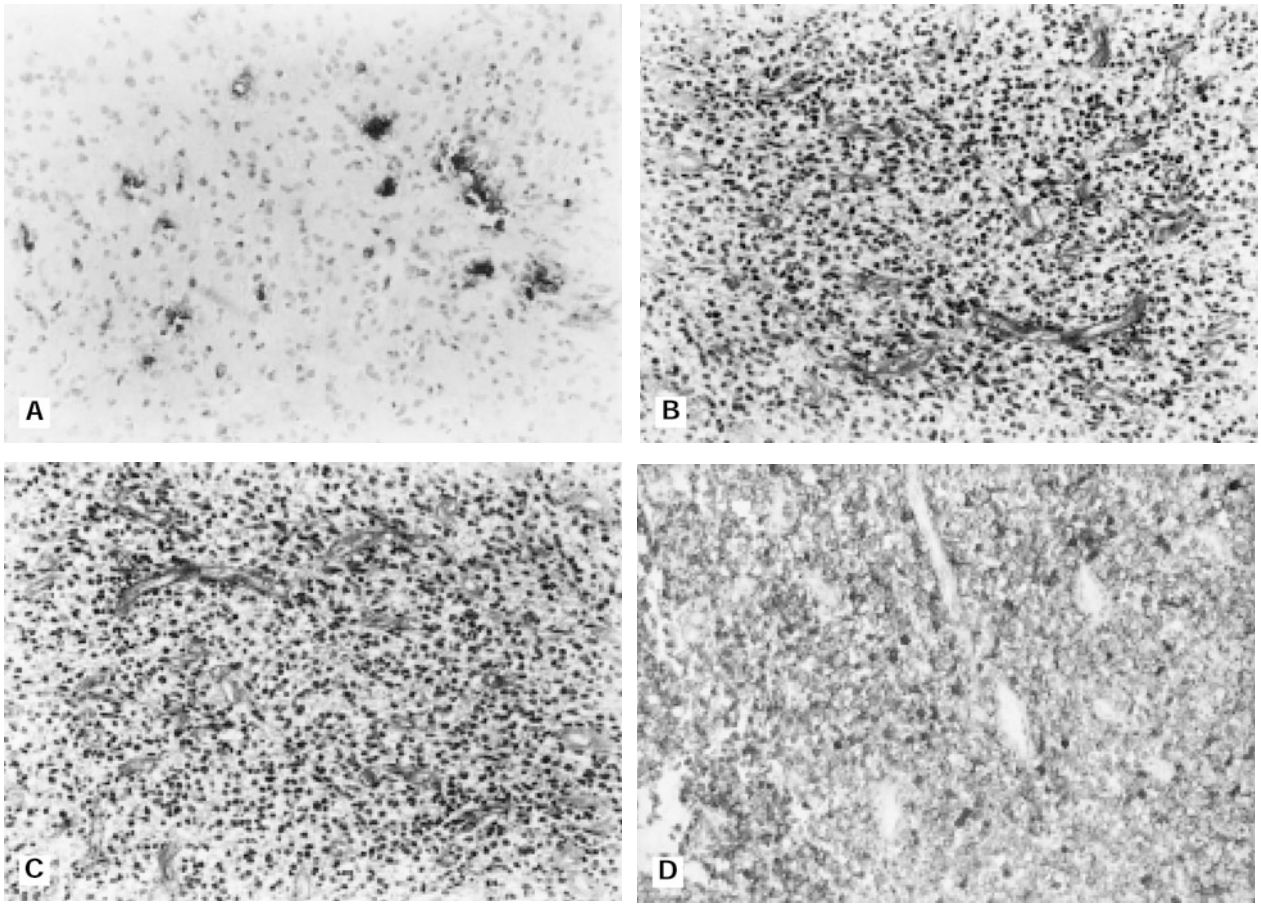

Fig. 3 - *Histological features. A) 1999 pituitary malignant tumor (x40), positive chromogranine A staining; B) 1999 frontal metastasis (x20) negative GFAP staining and positive chromogranine A staining; C) 1999 frontal metastasis (x20) negative hormonal immunostaining; D) retrospective analysis of the 1983 specimen (x20) positive hormonal immunostaining FSHβ.*

nomas were non-functioning and ACTH-producing tumors, whereas prolactinomas, well-known to be the most frequent tumors among benign tumors, were the third type (5). However, estimation of percentages for cases described during the last 5 years showed an increase of functional tumors (ACTH tumors and prolactinomas) with a drop in the number of non-functional tumors. Increase of functionality must be due to the routine serum prolactin assay and immunochemistry. However ACTH tumors remain the most frequent and confirm their first place [50% (16/32)] among other forms of secretion (Table 2). Obviously, many more cases than the last thirty-two cases recently described have to be reported to confirm this difference.

Carcinomas are known to be associated with poor prognosis (1, 29). They often disseminated and led to death within one year from diagnosis. Surgery and radiation therapy failed to significantly improve prognosis. When appropriate, essentially for functional tumors, more specific treatments such as dopamine agonists and somatostatin analogs may have been useful. However, such treatments have been shown to exert little influence in the progression of malignant pituitary tumors. Furthermore, response to chemotherapy was generally poor (3, 24). However, the last gonadotropic carcinoma (26) displayed a lower progression induced by chemotherapy.

Comparison with the previous cases described

Hence our case was a perfect example of the classical medical history and shared several characteristics with other pituitary carcinoma: first intervention from invasive macroadenoma many years earlier, adjuvant radiotherapy and delay of 15 years before carcinoma appears. Moreover, survival was short with metastases appearing suddenly only 5 months after the second radiotherapy. Central nervous system spread was consistent with the suprasellar localization of the primary tumor. This is the fourth gonadotropic pituitary carcinoma case described in the literature (5, 20, 26). Nevertheless, a number of pituitary carcinomas classified as non-functional could have been gonadotropic adenomas since no systematic immunocytochemistry was performed. Some unusual aspects are retrieved in one of these cases (20) such as the rich vascularization of the tumor. However, relapse time periods were very different in the three other cases, respectively 2 (20, 26) and 26 years (5) after both surgery and radiotherapy. Metastases occurred in one case (20) outside and inside of the brain and in the two others only inside it (5, 26). A particular feature of our case was the loss of differentiation of the tumor with time not found in the three other cases.

Table 2 - *Pituitary carcinomas described since 1904.*

Tumor type	1904/1995*	1996/2001**
ACTH (no.=37)	21 (26.5%) Nelson Sd)	16 (50%) (6 Nelson Sd)
PRL (no.=32)	21 (26.5%)	11 (34%)
NS (no.=26)	24 (30.3%)	2
GH (no.=13)	11 (14%)	2
FSH/LH (no.=3)	2	1
TSH (no.=1)	1	-
Total number: 112	80 (70+10)	32
Functional tumor percentage	56/80=70%	30/32=93%

*Majority of cases (70) described two reviews (4, 6); **new cases described in the last five years.

Histological support for diagnosis

A review of the previously reported cases repeatedly highlighted the failure of histological features such as mitotic activity and microinvasion to predict biological and tumoral behavior (9, 20, 21). In a pathological study (31) bearing on 60 adenomas with gradual aggressiveness, 26 pituitary adenomas, 28 invasive ones and 6 carcinomas, mitotic figures were found respectively in 3.9% for the former (1/26), 31.4% for the invasive ones (6/28) and 66.7% for the latter carcinomas (4/6). Mitotic figures were lacking in the majority of the pituitary tumors but their absence was insufficient to confirm benignity. Indeed, some lesions without mitotic figures at the beginning (as in our case) may have a malignant course. On the contrary, adenomas with mitotic features may never degenerate. In summary, mitotic activity score plays a limited role in the evaluation of biological aggressiveness in pituitary tumors. Providing pronostically relevant insight into the biological behavior of pituitary tumors, remained one of the foremost challenges confronting the pathologist to determine which tumors have the most invasiveness potential. In this respect, proliferation markers have been developed especially for endocrine tumors. This would help identify those patients who should be closely monitored and aggressively treated when carcinoma develops.

Assessment of mitotic index

Histological markers include Ki 67 determined by the MIB1 antibody, described as a good predictor of recurrence in pituitary tumors (1, 2, 3, 5, 12). Pernicone *et al.* (29) recommended use of a new classification with the identification of an intermediate state between adenoma and pituitary carci-

noma "AUMP" adenoma of uncertain malignant potential which illustrated a form of adenoma needing careful follow-up and including histological criteria with cellular marker described above. In our case, proliferator markers such ad Ki- 67 or PCNA were not used for the study of the 1999 specimen due to the highly mitotic index, showing evidence of malignancy. Ki 67 applied for the 1983 specimen showed no significant staining, emphasizing once again the limited role of pathological examination as predictive factor. However, tumor-aggressiveness was illustrated by loss of hormonal differentiation (negative FSH immunostaining in 1999 against a positive one in 1983). Loss of differentiation could have been underestimated in the literature. Because of relapse time, immunocytochemistry was not always available at the primary manifestation of the disease, as for one of the cases described earlier. Loss of differentiation of the tumors generally correlates with invasive and metastatic behavior. This behavior is well known in a number of endocrine tumors, for example thyroid carcinoma. Hormonal loss of differentiation could be one of the tools to develop, with routine plasmatic assay of hormonal precursor as POMC for ACTH tumors. The prognostic relevance of these markers awaits further investigation in the future.

Pathogenesis of the tumor: potential factors involved

The origin of pituitary carcinoma has been debated. It may be either right from the beginning an undiagnosed carcinoma with a low potential of development reactivated by surgery and radiotherapy or a transformation of a benign pituitary adenoma. Several lines of evidence suggest the occurrence of an adenoma to pituitary carcinoma sequence as loss of differentiation with time (29). It has been suggested that iterative surgery and radiotherapy may be involved in this transformation by analogy with the cerebral spread of "malignant" gliomas possibly induced by the surgery and by analogy to the occurrence of radiation induced tumors as meningiomas or sarcomas. However, use of these treatments could just reflect the aggressive behavior of these tumors. Genes, which participate in or provoke the development of pituitary carcinoma pathogenesis, are controversial. Alterations in tumor suppressor genes such as p-53, H-ras, and retinoblastoma have rarely been described (12). However, increased P53 staining may be a good marker of malignancy (29, 32). In one study (32), p53 positive staining was found in 100% of the pituitary carcinomas which were studied and was negative in 100% of pituitary non invasive adenomas (15% of positivity in invasive pituitary adenomas). In our case pituitary tumor p 53 immunostaining was also positive. In addition, C erbB-2, an oncoprotein displaying homology to the endothelial growth factor receptor has been described to be over-expressed in several tumors and in invasive pituitary macroadenoma (10).

CONCLUSION

In conclusion, we have described a pituitary carcinoma, which fulfills all required criteria for diagnosis. Our case emphasizes typical features of these rare tumors including relapse after iterative surgery and radiotherapy, and dramatic outcome. In contrast to previous cases, the primary tumor was a gonadotropic adenoma (fourth case described) exhibiting loss of differentiation with time. Indeed, the most frequent pituitary carcinomas are ACTH tumors. Nonetheless, systematic immunochemistry should reveal gonadotropic adenomas more frequently among the previous so called "non-functional", as the case described above. Due to the dramatic course of this disease it is necessary to describe each case in order to find predictive factors. This case emphasizes the need to improve diagnostic and prognostic tools as well as more efficient treatment. In this respect, further development of hormonal markers routine dosage, for example serum measurement of precursor such as POMC (for ACTH tumors), reflecting tumor differentiation could be useful. Further studies are required to investigate this assumption.

REFERENCES

1. Kemink S.A., Wesseling P., Pieters G.F.,Verhofstad A.A., Hermus A.R., Smals A.G.
   Progression of a Nelson's adenoma to pituitary carcinoma; a case report and review of the literature.
   J. Endocrinol. Invest. 1999, *22:* 70-75.
2. Takao M., Yoshokiyo A., Yukio I., Toshiharu I., Ikuko I., Toshio I., Tohru O., Hiromichi I., Noriko A.
   An ACTH-producing pituitary carcinoma developing Cushing's disease.
   Pathol. Res. Pract. 1999, *195:* 183-187.
3. Katsas G.A., Mukherjee. J.J., Monson P.N., Grossman A.B., Besser G.M.
   The role of cytotoxic chemotherapy in the management of agressive and malignant pituitary tumor.
   J. Clin. Endocrinol. Metab. 1998, *83:* 4233-4238.
4. Saeger W., Lubke D.
   Pituitary carcinomas.
   Endocrine Pathology 1996, *7:* 21-35.
5. O'Brien D.P., Phillips J.P., Rawluk D.R., Farrell M.A.
   Intracranial metastases from pituitary adenoma.
   Br. J. Neurosurg. 1995, *9:* 211-218.

6. Lubke D., Saeger W.
Carcinomas of the pituitary: definition and review of the literature.
Gen. Diagn. Pathol. 1995, *141:* 81-92.

7. Greenman Y., Woolf P, Coniglio J., Omara R., Pei L., Said J.W., Melmed S.
Remission of acromegaly caused by pituitary carcinoma after surgical excision of growth hormone secreting metastasis detected by 111-Indium pentetreotide scan.
J. Clin. Endocrinol. Metab. 1996, *81:* 1628-1633.

8. Lormeau B., Miossec P., Sibony M., Valensi P., Attaly J.R.
Adenocorticotropin-producing pituitary carcinoma with liver metastasis.
J. Endocrinol. Invest. 1997, *20:* 230-236.

9. De Boucaud L., Dousset V., Caillaud P., Viaud B., Guerin J, Caillé J.M.
Metastases from a pituitary adenoma: MRI.
Neuroradiology 1999, *41:* 785-787.

10. Alberti V.N., Mesquita M.I.S., Martin L.C., Kayath M.J.
Adrenocortcotropin-producing pituitary carcinoma with expression of c-erbB-2 and high PCNA index: A comparative study with pituitary adenoma and normal pituitary tissues.
Endocrine Pathology 1998, *9:* 53-62.

11. Popadic A., Witzmann A., Buchfelder M., Eiter H., Komminoth P.
Malignant prolactinoma: case report and review of the literature.
Surg. Neurol. 1999, *51:* 47-54.

12. Bayindir C., Balak N., Gazioglu N.
Prolactin-secreting carcinoma of the pituitary: clinicopathological and immunohistochemical study of a case with intracranial and intraspinal dissemination.
Br. J.I. Neurosurg. 1997, *4:* 350-355.

13. Della Casa S., Corsello S.M., Satta M.A., Rota C.A., Putignano P., Vangeli V., Colosimo C., Anile C., Barbarino A.
Intracranial and spinal dissemination of an ACTH secreting pituitary neoplasia. Case report and review of the literature.
Ann. Endocrinol. (Paris) 1997, *58:* 503-509.

14. Rockwell B.H., Pica R., Raji M.R., Dastur K.J., Altschuler E.M., Johnston J.M.
Intrathecal metastatic pituitary prolactinoma.
Am. J. Roentgenol. 1996, *5:* 1295-1296.

15. Matsuyama J., Mori T., Hori S.
ACTH producing pituitary adenoma with multiple intracranial metastases and spinal dissemination.
No Shinkei Geka 1995, *23:* 243-247.

16. Frost A.R., Tenner S., Tenner M., Rollhauser C., Tabbara S.O.
ACTH-producing pituitary carcinoma presenting as the cauda equina syndrome.
Arch. Pathol. Lab. Med. 1995, *119:* 93-96.

17. Long M.A., Colquhoun I.R.
Case report: multiple intra-cranial metastases from a prolactin-secreting pituitary tumour.
Clin. Radiol. 1994, *49:* 356-358.

18. Jamjoom A., Moss T., Coakham H., Jamjoom Z.A., Anthony P.
Cervical lymph nodes metastases from a pituitary carcinoma.
Br. J. Neurosurg. 1994, *8:* 87-92.

19. Gollard R., Kosty M., Cheney C., Copeland B., Bordin G.
Prolactin-secreting pituitary carcinoma with implants in the cheek pouch and metastases to the ovaries. A case report and literature review.
Cancer 1995, *76:* 1814-1820.

20. Beauchesne P., Trouillas J., Barral F., Brunon J.
Gonadotropic pituitary carcinoma: case report.
Neurosurgery 1995, *37:* 810-816.

21. Cartwright D.M., Miller T.R., Nasr A.J.
Fine-needle aspiration biopsy of pituitary carcinoma with cervical lymph node metastases: report of 2 cases and review of the literature.
Diagn. Cytopathol. 1994, *11:* 68-73.

22. Garrao A.F., Sobrinho L.G., Oliveira P., Bugalho M.J., Boavida J.M., Raposo J.F., Loureiro M., Limbert E., Costa I., Antunes J.L.
ACTH-producing carcinoma of the pituitary with haematogenic metastases.
Eur. J. Endocrinol. 1997, *137:* 176-180.

23. Richter M.L., Saeger W.,Leifke E., Fahlbusch R., von zur Muhlen A., Schuppert F.
A patient with an ACTH-producing pituitary tumor with liver metastases.
Dtsch. Med. Wochenschr. 2000, *298:* 52-56.

24. Mixson A. J., Friedman T. C., Katz D. A., Feuerstein I.M., Taubenberger J.K., Colandrea J.M., Doppman J.L., Oldfield E. H., Weinstraub B. F.
Thyrotropin-secreting pituitary carcinoma.
J. Clin. Endocrinol. Metab. 1993, *76:* 529-533.

25. Dayan C., Guilding T., Hearing S., Thomas P., Nelson R., Moss T., Bradshaw J, Levy A., Lightman S.
Biochemical cure of recurrent acromegaly by resection of cervical spinal canal metastases.
Clin. Endocrinol. 1996, *44:* 597-602.

26. McCutcheon I.E., Pieper D.R., Fuller G.N., Benjamin R.S., Friend K.E., Gagel R.F.
Pituitary carcinoma containing gonadotropins: treatment by radical excision and cytotoxic chemotherapy: case report.
Neurosurgery 2000, *46:* 1233-1239.

27. Ahmed M., Kanaan I., Alarifi A., Ba-Essa E., Saleem M.,Tulbah A., McArthur P., Hessler R.
ACTH-producing pituitary cancer: experience at the King Faisal Specialist Hospital and Research Centre.
Pituitary 2000, *3:* 105-112.

28. Arias M., Pereiro I., Requena I., Ventura M., Iglesias C., Lema C.
Malignant prolactinoma with intra- and extracranial metastasis: clinico-radiologic study
An. Med. Interna 2000, *17:* 192-194.

29. Pernicone P.J., Scheithauer B.W., Sebo T.J., Kovacs K.T., Horvath E., Young W.F., Loyd R.V., Davis D.H., Guthrie B.L., Schoene W.C.
Pituitary carcinoma: a clinicopathologic study of 15 cases.
Cancer 1997, *79:* 804-812.

30. Kasantikul V., Boonjunwetwat D., Suwangool P.
Prolactin cell carcinoma of the pituitary.
J. Med. Assoc. Thai. 1993, *76:* 230-237.

31. Thapar K., Yamada Y., Scheithauer B., Kovacs K., Yamada S. , Stefaneanu L.
Assesment of mitotic activity in pituitary adenomas and carcinomas.
Endocrine Pathology 1996, *7:* 215-221.

32. Thapar K.,Scheithauer B., Kovacs K., Pernicone P.J., Laws E.R.
p53 expression in pituitary adenomas and carcinomas: Correlation with invasiveness and tumor growth fraction.
Neurosurgery 1996, *384:* 763-770.

33. Petterson T., MacFarlane I.A., MacKenzie J.M., Shaw M.D.
Prolactin secreting pituitary carcinoma.
J. Neurol. Neurosurg. Psychiatry 1992, *55:* 1205-1206.

34. Tajika Y., Reifenberger G., Kiwit J.C., Wechsler W.
Metastatic adenocarcinoma in cerebral astrocytoma: clinicopathological and immunohistochemical study with review of the literature.
Acta Neurochir. (Wien) 1990, *105:* 50-55.

35. Mountcastle R.B., Roof B.S., Mayfield R.K., Mordes D.B., Sagel J., Biggs P.J., Rawe S.E.
Pituitary adenocarcinoma in an acromegalic patient: response to bromocriptine and pituitary testing: a review of the literature on 36 cases of pituitary carcinoma.
Am. J. Med. Sci. 1989, *298:* 109-118.