Brief Communication

Suppurative meningitis: A life-threatening complication in male macroprolactinomas

Farida Chentli, Lina Akkache, Katia Daffeur, Meriem Haddad, Said Azzoug

Department of Endocrinology and Metabolic Diseases, Bab El Oued Hospital, 5Boulevard Said Touati, Algiers, Algeria

ABSTRACT

Background: Suppurative meningitis (SM) or bacterial meningitis is a life-threatening condition, which is exceptionally due to pituitary tumors (PT). Our aim was to analyze its frequency among male macroprolactinomas (MPRL) deemed to be aggressive, to report the cases we observed in our practice and describe the circumstances under which SM appeared. **Materials and Methods:** We retrospectively analyzed 82 male MPRL in order to look for a history of well proved SM and the circumstances under which SM appeared. We also took into account the possibility of SM relapsing. **Results:** Four out of 82 male MPRL had SM = 4.87%. Three consulted for SM symptoms. SM was confirmed in Infectious Diseases department, but only one had rhinorrhea. Hormonal assessment and cerebral magnetic resonance imaging pleaded for aggressive prolactinomas. After antibiotics, SM was sterilized. Then, MPRL were treated with bromocriptine, which normalized prolactin and reduced PT. SM never relapsed. The 4th case was hospitalized for a large multidirectional prolactinoma invading and/or arising from the skull base. He was operated on 3 times and then he was given Bromocriptine. After 3 months, he had rhinorrhea and then SM which was successfully treated by antibiotics. SM never relapsed after tumor reduction. **Conclusion:** SM was demonstrated in 4.87%. SM has revealed MPRL in 3 cases and appeared after bromocriptine intake in the 4th one. Endocrinologists should be aware of this severe condition, which can be avoided by repairing as soon as possible the bony defect secondary to aggressive tumors, unless it is clogged by fibrosis: What probably happened in our cases.

Key words: Aggressive tumors, male prolactinomas, suppurative meningitis

Introduction

Male macroprolactinomas (MPRL) are usually revealed by headaches, visual troubles and gonadal insufficiency. Suppurative meningitis (SM), a life-threatening condition, is scarcely observed in subjects with macro tumors secreting prolactin (PRL) and in other pituitary tumors (PT).[1-12] However, in some very rare cases it can be a primary presentation or appear after radiotherapy or medical treatment used for tumors destroying the sellar floor and/or the skull base. This destruction leads to cerebral spinal fluid (CSF) leak, which can act as an entry portal for organisms predisposing to meningitis. Our aim was to analyze SM frequency among male MPRL deemed to be very invasive tumors, to report our cases and analyze the circumstances under which the dangerous neurological complication appeared.

Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.119524

Materials and Methods

In this retrospective study, we analyzed 82 subjects with MPRL to look for symptoms, clinical signs and biological proof of SM. These men were recruited between 1992 and 2012. In this study, we took into account medical history, clinical examination, routine exploration, CSF analysis and hormonal assessment. That one was based on PRL, growth hormone (GH), insulin growth hormone (IGF1), cortisol, adrenocorticotropic hormone, testosterone, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone and free thyroxin. Radiological assessment was based on cerebral computed tomography scan and/or magnetic resonance imaging (MRI). The follow-up after SM episode varied from 2 to 13 years.

Corresponding Author: Prof. Farida Chentli, Department of Endocrinology and Metabolic Diseases, Bab El Oued Hospital, 5Boulevard Said Touati, Algiers 16000, Algeria. E-mail: chentli.f@gmail.com

Results

Out of 82 male MPRL 4 had a history of SM = 4.87%. Three were first hospitalized in the department of Infectious Diseases for typical symptoms and signs of SM; that one was proved by CSF biochemical analyses. The fourth one was hospitalized in our department for the fourth episode of SM which was proved by CSF analysis after lumbar puncture.

The medical history of each patient was as follows:

Case Reports

Case 1

A man aged 22, consulted for vomiting and fever. SM diagnosis was confirmed by lumbar puncture and blood cultures. SM was successfully treated by antibiotics. Cerebral MRI showed a PT invading cavernous sinuses, the sphenoid sinus and the brain [Figure 1]. Hormonal assessment [Table 1] demonstrated high PRL with gonadotroph deficit. After antibiotics, SM was sterilized. Then, the PT was treated with dopamine agonists that were successful on PRL (25 ng/ml) and on tumor size [Figure 1]. After a follow-up of 7 years, SM never relapsed, although the sellar floor was not surgically repaired.

Case 2

A 49-year-old man was hospitalized in 2000 for the fourth SM. The previous ones were proved in 1984, 1988 and 1990. Clinical examination confirmed the meningeal syndrome and noticed rhinorrhea. Biochemical analyzes confirmed CSF leak and meningeal infection. The last one was treated successfully by antibiotics. Cerebral MRI showed an invasive and multidirectional PT measuring 47 mm × 40 mm × 30 mm destroying the sella floor and filling the sphenoid sinus [Figure 2]. The PT was secreting PRL [Table 1]. That one was normalized by bromocriptine and the tumor size was significantly reduced. 13 years after, there was not any SM relapsing.

Case 3

A man aged 25, with a history of chronic otitis and arrested puberty, was diagnosed as a multidirectional prolactinoma destroying the sella floor and measuring 30 mm × 30 mm × 30 mm [Figure 3]. The PT was responsible for optic atrophy, anterior pituitary insufficiency and diabetes insipidus. Pituitary lesion was diagnosed after SM due to pneumococcal infection. SM was sensitive to antibiotics. Under dopamine agonists PRL was normalized and the tumor volume decreased. After 2 years, there was not any SM relapsing.

Case 4

A 29-year-old man was sent to our unit for a prolactinoma revealed by epilepsy crises. The PT was very large (68 mm × 50 mm × 50 mm) and multidirectional with an extension to the chiasm, cavernous sinuses, posterior and nasal areas [Figure 4]. He was operated on 3 times in vain. Then he was given dopamine agonists, which normalized PRL and reduced the tumor. After 3 months he had rhinorrhea, then one episode of SM sterilized by antibiotics. SM never relapsed after a follow-up of over 2 years.

The Table 1 shows tumor sizes, hormonal parameters and bromocriptine dose which was used to treat the 4 prolactinomas.

Discussion

In the literature, there are few reports about SM in patients harboring PT. The life-threatening condition is deemed to be exceptional.[1-12] When it happens, it is usually observed in post-operative period or after tumor reduction by radiotherapy, apoplexy or medicine intake. The situation is observed in people in whom meninges and sella floor are destroyed by an aggressive PT or an ectopic one arising from the skull base.

Table1: Tumor size, hormonal assessment of our 4 patients, and bromocriptine dose used to reduce tumor volume and normalize prolactin.

Parameters	Case n° 1	Case n° 2	Case N°3	Case N°4
Tumor size (height x transversal diameter x anteroposterior diameter)	58x38x35mm	47 x40x30mm	30x30x30mm	68x50x50mm
PRL (<30ng/ml)	1821	1818	1781	14272
Testosterone (10.41-41.64nmol/l)	8.91	11.17	0.34	4.18
Follicle stimulating hormone: FSH (1-8mu/ml)	2.4	10.12	1.46	1.88
Luteinising stimulating hormone: LH (0.6-12mu/ml)	1.29	2.84	1.4	1.3
Cortisol (154-638nmol/l)	317.57	380.79	93	613.2
Free thyroxin: FT4 (8.02-24.5pmol/ml)	10.05	8.97	4.46	9.98
Thyroid stimulating hormone: TSH (0.2-4μU/ml)	1.5	0.51	/	/
Urinary gravity	1025	1020	1000	1015
Bromocriptine (mg/day)	15	25	15	20

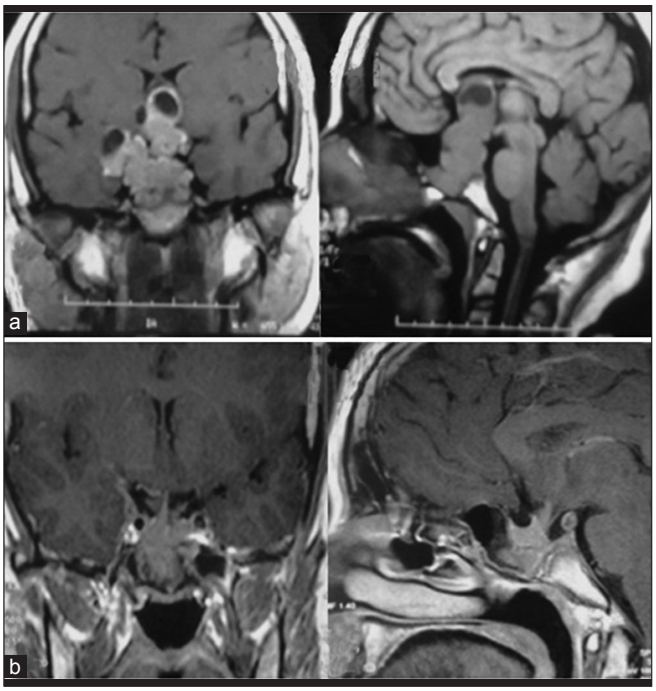

Figure 1: Invasive and aggressive pituitary tumor destroying the sella floor, responsible for suppurative meningitis (SM) in a 22-year-old man. (a) Before bromocriptine; (b) After treatment, bromocriptine intake and SM disappearance

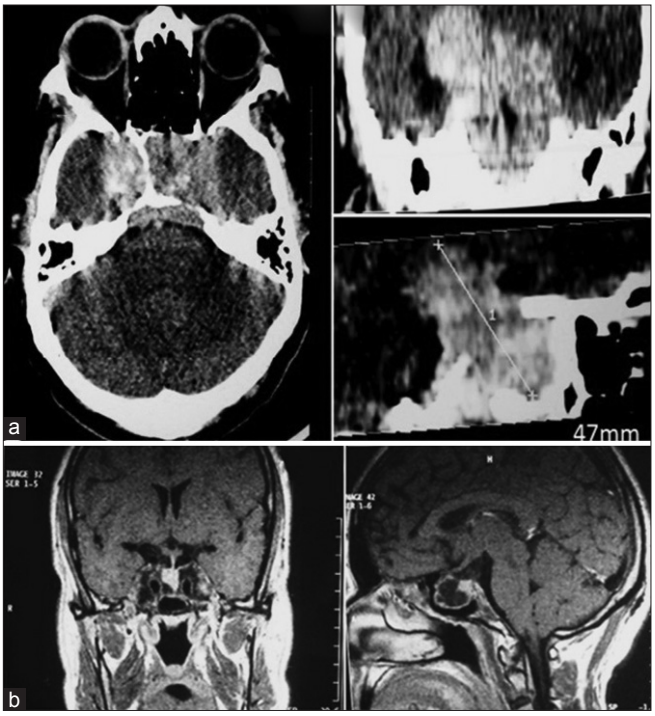

Figure 2: Large invasive tumor destroying the sella floor, responsible for suppurative meningitis in a 49-year-old man. (a) Before medical treatment; (b) Liquification of the tumor after bromocriptine

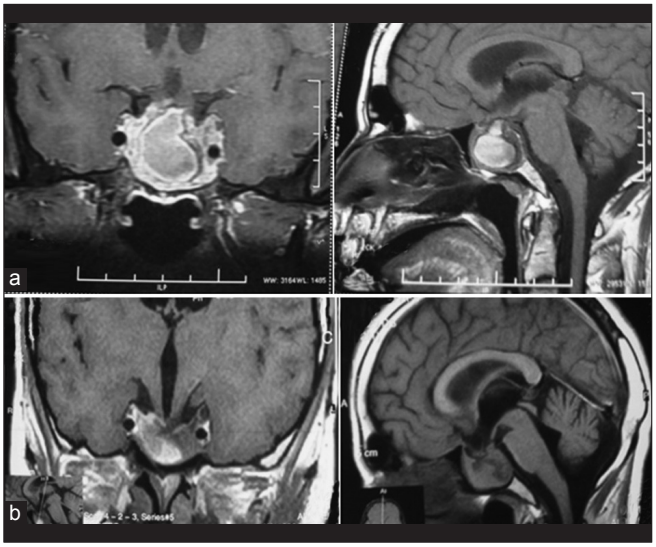

Figure 3: The pituitary tumor filling the sphenoid sinus before bromocriptine (a) and after bromocriptine (b)

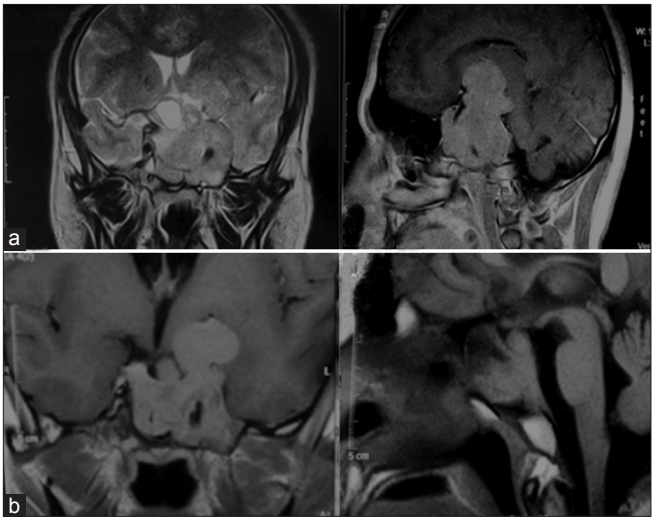

Figure 4: MRI showing a large tumor invading cavernous sinuses, the brain and sphenoid sinus (a). After dopamine agonists (b) the tumor size was reduced

Our 4 cases can be explained by the fact that prolactinomas are the largest and the most invasive PT, especially in males.[13] Male prolactinomas often destroy the sellar floor and invade the sphenoid sinus,[14] then the nasopharynx.[2] The meningeal and bony breaches lead to intra and extradural spaces communication, which is responsible for bacterial infection of meninges and encephalic structures.[1,2,11]

The most difficult differential diagnosis with meningitis occurring in people with PT is pituitary apoplexy, which mimics perfectly bacterial meningitis symptoms. Usually, aseptic meningitis characterizes pituitary apoplexy.[15,16] However, a real microbial meningitis with or without rhinorrhea can be observed in apoplexy.

The true microbial meningitis secondary to PT is an exceptional phenomenon compared to pituitary apoplexy, which is relatively more frequent. To our best knowledge

only 15 SM, revealing pituitary adenomas or appearing under medical treatment have been reported so far.[1-12] CSF leak may proceed or not SM, and can be totally unnoticed.

According to Lam *et al*. who analyzed 29 articles published between 1980 and 2011[17] there were only 52 PT with CSF leak. Among these cases only seven were complicated by bacterial cerebrospinal meningitis (13%). The seven cases were divided in two groups: The primitive meningitis or meningitis occurring prior to any treatment of the PT, and secondary meningitis occurring after surgery and/or dopamine agonists' intake as in our 4th observation.

Our personal research found 15 cases meningitis secondary to PT. If we add our 4 cases, one can totalize 19 cases. In this group most PT were prolactinomas, especially males ones. Among this group 14 were primitive. Secondary ones ($n = 5$) appeared under medical treatment, preceded or not by surgery or radiotherapy. Sellar floor destruction was obvious on radiographies in all except one case [Table 2].

Their age (varying between 22 and 69 years) did not seem to be a determining factor, but the nature of the adenoma and sphenoid sinus invasion seem fundamental. According to Ciatto[6] and to Lascelles *et al*.[5] non-functioning PT can also be associated to SM. We find only one case concerning GH adenoma[10] treated by somatostatin's analogs. A case of recurrent meningitis which appeared many years after neurosurgery was observed in Nelson syndrome too.[7] Curiously SM was not reported in mixed PT and gonadotroph adenomas which are usually very large and very invasive.

Contrary to many authors and in agreement with Ciatto,[6] we think the association of pituitary adenoma and meningitis is more common than it is generally supposed as we observed it in nearly 5% of our male MPRL. So, one should think about it more often even if a cause of SM seems obvious from the first sight as in our 4th case who suffered from chronic otitis. Radiological research for PT should be systematic, especially if headaches, visual troubles, and gonadal abnormalities with or without anterior or posterior pituitary deficiencies are present.[11,15-18] Physicians who deal with large PT should be aware of high risk spontaneous meningitis, but also of secondary SM which can appear 1 month to 4 years or even more[9] after medical treatment initiation by dopamine agonists or somatostatin's analogs or radiotherapy. On another hand, medical treatment initiation should be gradual, especially for huge tumors as rapid shrinkage may lead to CSF leak apparition. If this situation appears, a medical solution may be tried using temporary lumbar puncture or a lumboperitoneal shunt until the bony defect is clogged by fibrosis. If this attitude fails, surgical repair is recommended[17] although the reparation may represent a great challenge because of the many potential sites of the CSF around the tumor.[19] If surgical repair in not feasible some authors recommend a vaccination against pathogens of the upper respiratory tract such as

Tableau 2: Our patients characteristics compared to the 15 cases reported in literature.

Cases	Sexe	Age (years)	Apparition	Sellar floor destruction	Nature of the pituitary tumor
Lascelles *et al* 1973	M	45	Spontaneous	Yes	Non functioning
	M	48	Spontaneous	Yes	Non functioning
Ciatto 1978	?	?	Spontaneous	?	Non functioning
	?	?	Spontaneous	?	Non functioning
Flad *et al* 1991	F	?	9 years after surgery	Yes	Nelson Syndrome
	?	?	Bromocriptine	yes	Prolactinoma
Onada *et al* 1992	M	44	Spontaneous	Yes	Prolactinoma
Stephenson *et al* 2001	M	31	Spontaneous	yes	Prolactinoma
Wood *et al* 2002	M	33	Bromocriptine/ Cabergoline.	Yes	Prolactinoma
Utsuki *et al* 2004	M	69	Spontaneous	No	Prolactinoma
Onegger *et al 2009*	M	64	Spontaneous	Yes	Prolactinoma
Tan *et al* 2010	F	41	Spontaneous	Yes	Prolactinoma
	F	38	Surgery, Radiotherapy, Lanreotide	Yes	Somatotroph adenoma
Robert *et al* 2010	F	32	Spontaneous	Yes	Prolactinoma/non functioning? (PRL=84ng/ml)
Andrysiak-Mamos *et al 2013*	M	30	Spontaneous	Yes	Prolactinoma
Chentli *et al* 2013	M	22	Spontaneous	Yes	Prolactinoma
	M	49	Spontaneous	Yes	Prolactinoma
	M	25	Spontaneous	Yes	Prolactinoma
	M	29	Bromocriptine	Yes	Prolactinoma

streptococcus pneumonia, haemophilus influenza and Neisseria meningitidis to prevent SM.[9]

Conclusion

In this study, SM was observed in 4.87% among male MPRL. Three revealed the PT, and one was observed after medical treatment. In 2 cases rhinorrhea was totally unnoticed.

The described cases emphasize the necessity of an early diagnosis and treatment of large and invasive PT, especially male MPRL. Medical treatment, which is now the gold standard for prolactinomas, should be gradual and well monitored to avoid rhinorrhea or otorrhea which can lead to potentially fatal bacterial meningitis.

References

1. Laszewski MJ, Moore SA. Occult invasive pituitary adenoma predisposing to fatal bacterial meningitis. Clin Neuropathol 1990;9:101-5.
2. Onoda N, Kamezu Y, Takagi S, Shinohara Y, Osamura RY. An autopsy case of invasive pituitary adenoma (prolactinoma) with rapid fatal clinical course due to streptococcal meningitis. Acta Pathol Jpn 1992;42:832-6.
3. Utsuki S, Oka H, Tanaka S, Iwamoto K, Hasegawa H, Hirose R, *et al.* Prolactinoma with a high adrenocorticotropic hormone level caused by meningitis: Case report. Neurol Med Chir (Tokyo) 2004;44:86-9.
4. Honegger J, Psaras T, Petrick M, Reincke M. Meningitis as a presentation of macroprolactinoma. Exp Clin Endocrinol Diabetes 2009;117:361-4.
5. Lascelles RG, Tuck SJ, Bhalla KK, Graves PS. Meningitis as the presenting symptom of pituitary adenomata. Postgrad Med J 1973;49:362-4.
6. Ciatto A. Clinical onset of meningitis in chromophobe adenoma of the pituitary: 2 cases. Minerva Med 1978;69:1325-9.
7. Fiad TM, McKenna TJ. Meningitis as a late complication of surgically and medically treated pituitary adenoma. Clin Endocrinol (Oxf) 1991;35:419-22.
8. Stephenson I, Wiselka MJ. An unusual cause of acute bacterial meningitis. Postgrad Med J 2001;77:791, 800-1.
9. Wood R, Sandeman DD, Gawne-Cain ML, Holt RI. Meningitis four years after treatment of macroprolactinoma. J R Soc Med 2002;95:501-2.
10. Tan HK, Jayashekara J, Flanagan D. Two cases of meningitis as a complication of pituitary adenoma. Clinical cases of British endocrine society. Endocr Abstr 2010; 21:193.
11. Robert T, Sajadi A, Uské A, Levivier M, Bloch J. Fulminant meningoencephalitis as the first clinical sign of an invasive pituitary macroadenoma. Case Rep Neurol 2010;2:133-8.
12. Andrysiak-Mamos E, Sagan L, Sowinska-Przepiera E, PobłockI J, Kazmierczyk-Puchalska A, Małgorzata Zajac-Marczewska M, *et al.* Cerebrospinal meningitis in 30-year-old man as first manifestation of pituitary macroadenoma. Endocrine Abstracts 2013;32:244.
13. Delgrange E, Trouillas J, Maiter D, Donckier J, Tourniaire J. Sex-related difference in the growth of prolactinomas: A clinical and proliferation marker study. J Clin Endocrinol Metab 1997;82:2102-7.
14. Hanel RA, Prevedello DM, Correa A, Antoniuk A, Araújo JC. Cerebrospinal fluid fistula as the presenting manifestation of pituitary adenoma: Case report with a 4-year follow-up. Arq Neuropsiquiatr 2001;59:263-5.
15. Cagnin A, Marcante A, Orvieto E, Manara R. Pituitary tumor apoplexy presenting as infective meningoencephalitis. Neurol Sci 2012;33:147-9.
16. Huang WY, Chien YY, Wu CL, Weng WC, Peng TI, Chen HC. Pituitary adenoma apoplexy with initial presentation mimicking bacterial meningoencephalitis: A case report. Am J Emerg Med 2009;27:517.e1-4.
17. Lam G, Mehta V, Zada G. Spontaneous and medically induced cerebrospinal fluid leakage in the setting of pituitary adenomas: Review of the literature. Neurosurg Focus 2012;32:E2.
18. Jeon BC, Park YS, Oh HS, Kim YS, Chun BK. Pituitary apoplexy complicated by chemical meningitis and cerebral infarction. J Korean Med Sci 2007;22:1085-9.
19. Little AS. Repair of Cerebrospinal Fluid Fistula from an Invasive Skull Base Prolactinoma Using a Septal Mucosal Vascularized Flap: Technical Case Report. J Neurol Surg A Cent Eur Neurosurg 2013; [Epub ahead of print].

Cite this article as: Chentli F, Akkache L, Daffeur K, Haddad M, Azzoug S. Suppurative meningitis: A life-threatening complication in male macroprolactinomas. Indian J Endocr Metab 2013;17:S117-21.

Source of Support: Nil, **Conflict of Interest:** None declared.