Journal of Medical & Surgical Pathology

Guadagno et al., J Med Surg Pathol 2016, 1:2
DOI: 10.4172/2472-4971.1000113

Case Report Open Access

A Granulomatous Hypophysitis "Consequent" to a Silent ACTH Cell Adenoma: A Case Report

Elia Guadagno[1*], Mariarosaria Cervasio[1], Alberto Di Somma[2], Luigi Maria Cavallo[2] and Marialaura Del Basso De Caro[1]

[1]*Department of Advanced Biomedical Sciences, Pathology Section, University of Naples Federico II, Italy*

[2]*Department of Neurosciences and Reproductive and Odontostomatological Sciences, Division of Neurosurgery, University of Naples Federico II, Italy*

[*]**Corresponding author**: Elia Guadagno, Department of Advanced Biomedical Sciences, Pathology Section, University of Naples Federico II, Italy Via Pansini 5, Italy, Tel: +39 081 7463433 ; Fax: +39 081 7463475; E-mail: eliaguadagno84@gmail.com

Received date: February 03, 2016; **Accepted date**: March 09, 2016; **Published date**: March 14, 2016

Abstract

Herein is described a rare association of granulomatous hypophysitis and a silent corticotroph macroadenoma, observed in a 50- year-old male who came to the attention of the clinicians with a history of frontal headache.

Silent adenomas account for about one quarter of the pituitary adenomas and are characterized by the lack of a characteristic clinical syndrome or serum hormone marker. A granulomatous pituitary inflammatory reaction can be caused by systemic tuberculosis, syphilis, fungal infections or be idiopathic. The coincidence of these two conditions is known in the literature and a few hypotheses have been advanced concerning their relationship. The aim of our report was to scrutinize any possibility of causality that could explain this phenomenon. The ultimate goal was trying to understand a possible prognostic significance of the inflammatory reaction to neoplastic proliferation if there were any.

Keywords: Granulomatous hypophysitis; Pituitary; Adenoma; Silent

Introduction

Pituitary inflammatory lesions are uncommon: a granulomatous inflammatory reaction can be caused by systemic tuberculosis, syphilis or fungal infections, being usually an incidental autopsy finding [1]. They come to the pathologist more frequently when they are at an advanced stage, producing a mass effect and/or hypothalamic. However, the most enigmatic form of granulomatous hypophysitis is idiopathic.

Exceptional is the association of this inflammatory lesion with adenomatous neoplastic one. The aim of our report was to make assumptions on the pathogenesis of this unlikely association.

Case Report

We report the case of a 50-year-old male with a history of frontal headache lasted for years. In the last three years he had noticed an unexplained weight gain, decreased libido and sporadic visual defects.

For this reason, he went to an eye doctor who suggested to make a magnetic resonance (MRI) of the brain which revealed an intrasellar tumor with slight suprasellar extension, displaying areas of hemorrhage and necrosis, most likely a pituitary macroadenoma. A computerized examination of the visual field highlighted a temporal hemianopsia of the left eye.

Therefore, he was admitted to the department of neurosurgery. On clinical examination, a grade I obesity was found. Hormonal measurements showed normal levels but a slight increase of prolactin.

The patient underwent surgery and the tumor was removed via an endoscopic endonasal approach. In the post-operative course, a conspicuous improvement of visual functions was observed. 24 months after surgery the patient's conditions were stable.

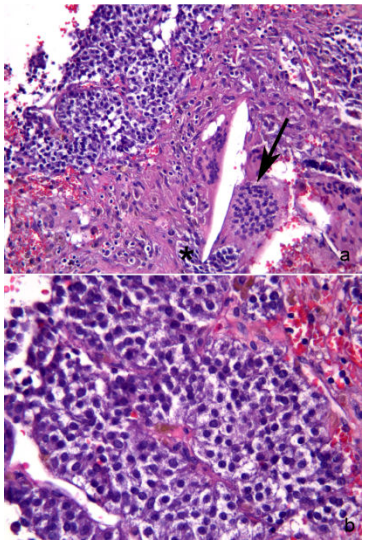

Figure 1: (a) Mainly at the periphery of the adenoma, a granulomatous reaction was detected (right). In this field, a small nodule of adenomatous cells (*) was surrounded by a cholesterol cleft and multiple multinucleated giant cells (arrow). (Haematoxylin and eosin stain, 200x): (b) Adenomatous cells displayed monotonous round-oval nuclei and faintly basophilic cytoplasm. (Haematoxylin and eosin stain, 400x).

The surgical specimen was taken to the department of pathology where it was analyzed for diagnosis.

Microscopically we observed, within a wide necrobiotic context, a proliferation of faintly basophilic neoplastic cells displaying a diffuse growth pattern, with a disrupted reticulin fibers network and a mild nuclear pleomorphism.

At the periphery of the lesion, a non-caseating granulomatous reaction was evident and consisted of macrophages and multinucleated giant cells (CD68+, CD1a-, S100-) around cholesterol clefts (Figure 1), mixed with a significant proportion of CD8+ T cells (Figure 2).

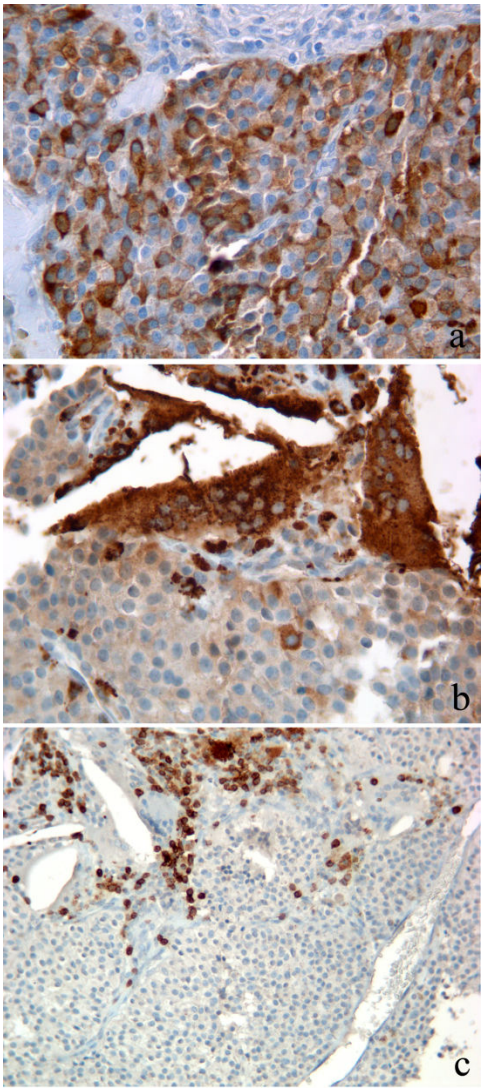

Figure 2: (a) Neoplastic cells were immunoreactive for ACTH (400x); (b) Macrophages and multinucleated giant cells were highlighted with CD68 immunostaining (400x); (c) A significant proportion of cells belonging to the inflammatory infiltrate were CD8+Tcells (200x).

Neoplastic cells exhibited variable immunoreactivity for ACTH (Figure 2) and expressed a low cellular proliferating index KI67/MIB1 (2%). All other pituitary hormones (GH, PRL, TSH, LH and FSH) were negative.

These aspects were consistent with a diagnosis of "silent" ACTH cell adenoma associated with granulomatous hypophysitis.

At ultrastructural examination, tumor cells were characterized by abundant secretory granules, highly variable in size, shape and electron density and were devoid of cytoplasmic intermediate filaments (4000x) (Figure 3). It was a silent corticotroph adenoma-type II, associated with granulomatous hypophysitis.

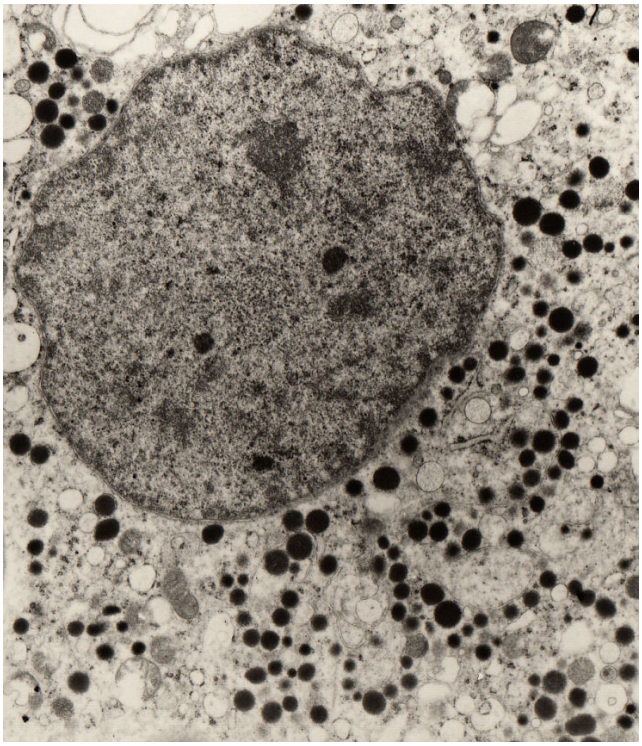

Figure 3: Ultrastructural examination: tumor cells were characterized by abundant secretory granules, highly variable in size, shape and electron density and were devoid of cytoplasmic intermediate filaments (4000x).

Methods

Surgical specimen was fixed in buffered formalin and embedded in paraffin. Immunohistochemistry was performed using the avidin biotin complex (ABC) as system of visualization and the diaminobenzidine as chromogen for the reaction with polyclonal antibodies against GH (Cell Marque; 208A-78), PRL (Cell Marque; 210A-18), FSH (Cell Marque; 207A-78), LH (Cell Marque; 209A-18), TSH (Cell Marque; 211A-18), ACTH (Cell Marque; 206A-74) and S100 protein (Ventana, 760-2523) and monoclonal antibodies against Ki67 (MIB1-Dako; M7240), CD8 (SP57, Ventana; 790-4460), CD4 (SP35, Ventana; 790-4423), CD3 (2GV6, Ventana; 790-4341), CD68 (KP1, Ventana; 790-2931) and CD1a (EP3622, Ventana; 760-4525).

For electron microscopy, a small sample was fixed in glutaraldehyde and then in osmium tetroxyde for embedding in Epon 812. Ultrathin sections were collected on 100-mesh copper grids and double-stained

with uranyl acetate and lead citrate. Sections were examined in a Zeiss 900 transmission electron microscope.

Discussion

The coexistence of two lesions in the pituitary is well-known in literature: cases of multiple adenomas, namely separate associated lesions mimicking a plurihormonal lesion, are reported [2], as well as cases of craniopharyngiomas or Rathke cysts associated with adenomas [3,4].

In our case, the coexistence was of an inflammatory and a neoplastic lesion, as granulomatous hypophysitis and adenoma. Only a few cases have been reported [5-8] and in most of them the adenoma was silent, exactly as in the present case.

Therefore the question is: should this association be considered non-coincidental?

An eventuality is that the adenoma coexisted with a rathke cyst that, after having ruptured, may have led a granulomatous reaction without leaving any residue of the cyst [6,9]. In the present case, no epithelial residues or mucus had been observed but cholesterol clefts which are typically found in craniopharyngiomas. It is unlikely that the adenoma could coexist with a craniopharyngioma whose only track was the granulomatous reaction.

To date 8 cases of pituitary adenomas coexistent with granulomatous reaction have been described and among these 7 were not functioning. Therefore, there may be reason to believe that this association is not coincidental and that the presence of a ruptured cyst cannot be deemed a sufficient explanation, considering the rarity of this eventuality and the fact that the adenoma is practically always a silent form (7 cases out of 8).

Another hypothesis is that the xanthogranulomatous reaction is triggered by hemorrhage: it is known that silent-ACTH -adenomas have a peculiar tendency to develop hemorrhagic infarction [10]. Intratumoral hemorrhage is a frequent finding and it is highly improbable that it may play a role in the formation of granulomatous lesions, considering the infrequence of their association.

Granulomas form when the immune system attempts to wall off substances that perceives as foreign but is unable to eliminate. Such substances include infectious organisms including bacteria and fungi, or other materials such as keratin and suture fragments. The definition of a granuloma is difficult [11]; conceptually it evolves in three stages: the infiltration of young mononuclear phagocytes, their maturation, and their aggregation into a mature granuloma (foreign body granuloma). Giant cells of the foreign body type arise by fusion of either macrophages or epithelioid cells. Agents able to evoke a granulomatous reaction are likely to be persistent, particulate substances capable of producing modest maturation of macrophages.

A causal role of the tumor to develop a granulomatous reaction has already been described in cases of extracerebral neoplasms [12-14], mostly carcinomas, rarely sarcomas [15]. The morphology of tumor-related and infection-related granulomas is always indistinguishable: what they have in common is the heavy presence of γ/ΔT cells [16]. These latter release tumor necrosis factor-α, interferon-γ and granulocyte-macrophage colony stimulating factor, exerting cytotoxic activity. Besides the use of anti-γ/anti-Δ immunostaining (not commonly available, cytotoxic T cells can be highlighted by CD8 immunohistochemical marker. In our case, the inflammatory infiltrate was rich of CD8+T cells. In this context, also the use of antibodies anti Interleukin-2 and Interleukin-15 would have been useful in highlighting the environment favorable for activation and maturation of CD8 (+) T cells, but both these antibodies are not available in daily practice.

The significance of this inflammatory reaction could be that to prevent the extent of the tumor, as reported in several types of malignant neoplasms as part of a spontaneous regression process [17]; the exclusivity in our case was that pituitary adenomas belong to a category of histologically benign tumors. Since not all clinically non-functioning macroadenomas are characterized by a so heavy granulomatous reaction, we can hypothesize that this aspect is a possible expression of a different biological behavior. In our case the course was uneventful after 24 months from surgery. Not known is the trigger for the cytotoxic reaction.

Silent corticotroph adenomas express the POMC gene and its splicing products, are immunoreactive for β-endorphin and release ACTH-like substances in vitro. Tissue cultures could be applied to judge whether or not these substances are able to trigger a granulomatous reaction.

Conclusion

We reported a rare case of coexistence of granulomatous hypophysitis and silent macroadenoma. Its existence has been well-known for years but nobody never stressed the possibility of a causal link between them, as noted in several extracranial tumors. The peculiarity also stands on the tumor type, benign and endocrine, thus not properly epithelial [12-14]. We believe that the significance of this association should be verified, in order to clarify its impact on prognosis and eventually on the treatment strategies.

Conflict of Interests

The authors declare that they have no conflict of interest.

Author's Contribution

EG drafted the manuscript and helped carrying out the histologic evaluation, MC carried out the study of electron microscopy and interpretation of results, AD provided clinical information and helped drafting the manuscript, LMC was the surgeon and supervised this manuscript, MDBDC carried out the histological evaluation and supervised this manuscript. All the authors read and approved the final manuscript.

Acknowledgements

All the authors have substantively contributed to the realization of the manuscript and gave permission to be named. No person not named in the manuscript has made substantial contributions to this manuscript to warrant inclusion in the Acknowledgments. We would like to thank Adelia Rivelli for the revision of the English language.

References

1. Rickards AG, Harvey PW (1954) Giant-cell granuloma and the other pituitary granulomata. Q J Med 23: 425-439.
2. Jastania RA, Alsaad KO, Al-Shraim M, Kovacs K, Asa SL (2005) Double adenomas of the pituitary: transcription factors Pit-1, T-pit, and SF-1 identify cytogenesis and differentiation. Endocr Pathol 16: 187-194.

3. Finzi G, Cerati M, Marando A, Zoia C, Ferreli F, et al. (2014) Mixed pituitary adenoma/craniopharyngioma: clinical, morphological, immunohistochemical and ultrastructural study of a case, review of the literature, and pathogenetic and nosological considerations. Pituitary 17: 53-59.
4. Karavitaki N, Scheithauer BW, Watt J, Ansorge O, Moschopoulos M, et al. (2008) Collision lesions of the sella: co-existence of craniopharyngioma with gonadotroph adenoma and of Rathke's cleft cyst with corticotroph adenoma. Pituitary 11: 317-323.
5. Holck S, Laursen H (1983) Prolactinoma coexistent with granulomatous hypophysitis. Acta Neuropathol 61: 253-257.
6. Saeger W, Hofmann BM, Buslei R, Buchfelder M (2007) Silent ACTH cell adenoma in coincidence with granulomatous hypophysitis--a case report. Pathol Res Pract 203: 221-225.
7. Scheithauer BW, Silva AI, Atkinson JL, Nippoldt TB, Kaufmann TJ, et al. (2007) Pituitary adenoma with tumoral granulomatous reaction. Endocr Pathol 18: 86-90.
8. Nishioka H, Shibuya M, Ohtsuka K, Ikeda Y, Haraoka J (2010) Endocrinological and MRI features of pituitary adenomas with marked xanthogranulomatous reaction. Neuroradiology 52: 997-1002.
9. Amano K, Kubo O, Komori T, Tanaka M, Kawamata T, et al. (2013) Clinicopathological features of sellar region xanthogranuloma: correlation with Rathke's cleft cyst. Brain Tumor Pathol 30: 233-241.
10. Scheithauer BW, Jaap AJ, Horvath E, Kovacs K, Lloyd RV, et al. (2000) Clinically silent corticotroph tumors of the pituitary gland. Neurosurgery 47: 723-729.
11. Adams DO (1976) The granulomatous inflammatory response. A review. Am J Pathol 84: 164-192.
12. Hes O, Hora M, Vanecek T, Sima R, Sulc M, et al. (2003) Conventional renal cell carcinoma with granulomatous reaction: a report of three cases. Virchows Arch 443: 220-221.
13. Ouellet S, Albadine R, Sabbagh R (2012) Renal cell carcinoma associated with peritumoral sarcoid-like reaction without intratumoral granuloma. Diagn Pathol 7: 28.
14. Tajima S, Koda K (2015) Granulomatous inflammation of pulmonary squamous cell carcinoma: a rare phenomenon. Int J Clin Exp Pathol 8: 7547-7552.
15. Brincker H (1986) Sarcoid reactions in malignant tumours. Cancer Treat Rev 13: 147-156.
16. Zhao X, Wei YQ, Kariya Y, Teshigawara K, Uchida A, et al. (1995) Accumulation of gamma/delta T cells in human dysgerminoma and seminoma: roles in autologous tumor killing and granuloma formation. Immunol Invest 24: 607-618.
17. Gregorie HB, Othersen HB, Moore MP (1962) The significance of sarcoid-like lesions in association with malignant neoplasms. Am J Surg 104: 577-586.