

Pheochromocytoma in Regions of Central TUNISIA: Epidemio-Clinical and Anatomopathological Aspects of 47 Cases

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Abstract

Objectives: describe the epidemiological, clinical and anatomopathological aspects of this tumor in central Tunisia. **Method:** This was a retrospective descriptive study of histologically diagnosed cases of pheochromocytoma from January 1993 to December 2023, collected in the cancer registry of central Tunisia. **Results:** We collected 47 cases of pheochromocytoma with an average of 1.52 cases/year. The mean age was 48.06 years. The sex ratio was 0.68. It was most often discovered in the presence of a tumor syndrome (57.50%) with arterial hypertension (37.50%) and Menard's triad (27.50%). Only total adrenalectomy specimens were referred, 6.38% of which were extended to the kidney. The left adrenal gland was most affected in 56.52% of cases. On gross examination, the tumor had a mean size of 6.92 cm. It was usually well limited (91.67%), encapsulated (84.85%), greyish (53.85%), friable (50%), with hemorrhagic (65.97%). Histologically, 65.96% of cases were potentially non-aggressive, 34.04% aggressive and 4.25% metastatic. It was composite in 4.25% with a ganglioneuroma component. Stage II was most common in 63.6%. Immunohistochemical confirmation was performed in 59.57%. **Conclusion:**

Pheochromocytoma is rare in central Tunisia. It mainly affects adult women. It is usually non-aggressive and diagnosed at a localized stage. Studies of the genetic are recommended.

Keywords

Pheochromocytoma, Anatomopathological, Central Tunisia

1. Introduction

Pheochromocytoma is a neuroendocrine tumor derived from chromaffin cells in the adrenal medulla [1]. It is rare and may be discovered incidentally, referred to as an adrenal incidentaloma. It is sometimes symptomatic, causing high blood pressure or Menard's triad [2]. Pheochromocytomas are often non-aggressive, but approximately 10 to 15% are metastatic. A definitive diagnosis is made by pathological examination [3].

Given the rarity and challenges of pathological diagnosis of this tumor, we have undertaken this study with the aim of investigating the epidemiological, clinical, and anatomopathological aspects of pheochromocytoma.

2. Materials and Methods

This was a retrospective, descriptive study conducted over a 31-year period from January 1, 1993, to December 31, 2023.

It was carried out in the Tunisian Cancer Registry (RCCT), which covers the central-eastern and central-western regions of Tunisia.

The study included histologically confirmed cases of pheochromocytoma in central Tunisia. Cases without histological confirmation by a pathology report recorded in the cancer registry were excluded.

The parameters studied were frequency, age, sex, tumor location, circumstances of discovery, cancer history, and macroscopic, histological, and immunohistochemical aspects. The PASS score, established in 2002 to assess tumor aggressiveness and metastatic potential, was studied. It was specified in the pathology report or assessed based on the presence or absence of these 12 items rated +1 or +2: peri-adrenal adipose invasion +2; > 3 mitoses/10 high power fields +2; atypical mitoses +2; necrosis +2; cellular spindling +2; marked nuclear pleomorphism +1; cellular monotony +2; large nests or diffuse growth +2; high cellularity +2 capsular invasion +1; vascular invasion +1; nuclear hyperchromatic +1. A score of ≥ 4 is classified as aggressive. These were obtained from cancer registry records and pathological reports.

3. Results

We collected a total of 47 cases of pheochromocytoma, representing an annual frequency of 1.52 cases, with extremes ranging from 0 to 5 cases. Females were the

most represented gender, accounting for 59.57% of cases, with a sex ratio of 0.68. The average age of patients was 48.06 years, ranging from 26 to 79 years. The 41-50 age group was the most affected, accounting for 42.22% of cases. Left adrenal involvement was predominant, accounting for 56.52% of cases.

A personal history of cancer was noted in 12.76% of cases, consisting of carotid paraganglioma (6.38%), medullary thyroid carcinoma (4.26%), and non-specific invasive breast carcinoma (2.13%). There was no family history of cancer.

The tumor was discovered due to symptoms in 82.50% of cases, notably an abdominal mass (57.50%), high blood pressure (37.50%), and Menard's triad (27.50%). The composite pheochromocytoma had no specific manifestations. It was responsible for Menard's triad. Incidentalomas were noted in 17.50% of cases, in the context of renal colic (7.50%), hepatic hydatid cyst (7.50%), and breast cancer (2.50%).

All specimens were total adrenalectomy specimens, of which 6.38% were enlarged to the kidney (**Figure 1**) and 2.13% were associated with a partial hepatectomy specimen. The average tumor size was 6.92 cm, ranging from 1.7 cm to 15 cm. The tumor was well-defined (91.67%) and encapsulated (84.85%). It was grayish in 53.85% of cases, brownish in 26.64% of cases, and yellowish in 20.51% of cases. It was friable (50%), soft (37.5%), and firm (12.5%). The tumor showed hemorrhagic (65.97%), cystic (23.40%), necrotic (19.15%), and myxoid (4.25%) changes.

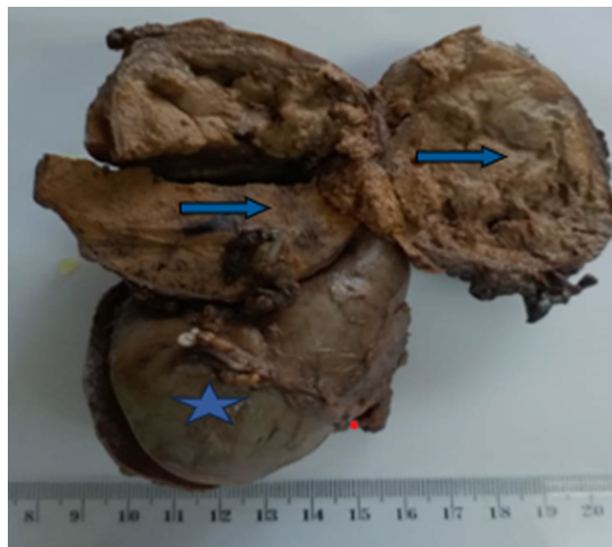


Figure 1. Macroscopic image of a specimen from a total adrenalectomy enlarged to include the kidney: showing a large, fleshy adrenal mass with hemorrhagic and necrotic changes (arrow). Kidney (star).

The tumor architecture was trabecular (93.62%), alveolar (53.19%), insular (8.51%), diffuse (6.38%), and massive (4.25%) (**Figure 2**). The stroma was endocrine-like in 100% of cases. There were 4.25% cases of ganglioneuroma-type composite pheochromocytoma.

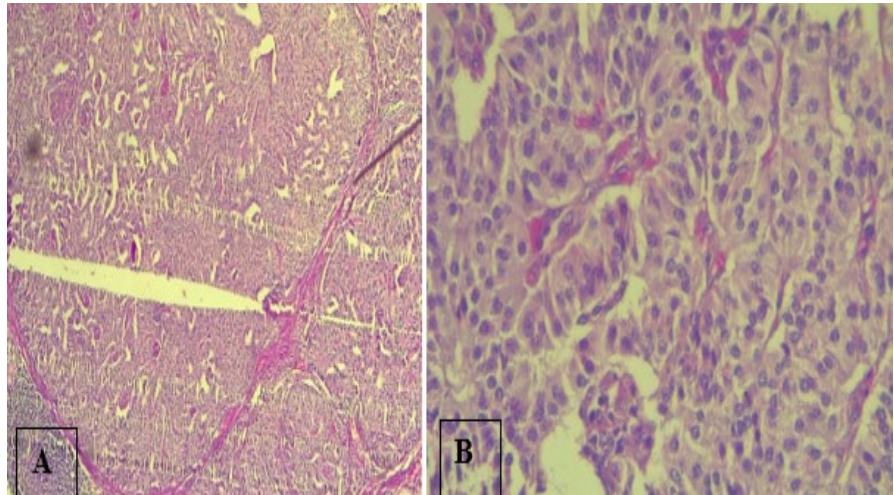


Figure 2. Histological images of a non-aggressive pheochromocytoma. A: HE, $\times 40$: encapsulated and hypervascularized tumor proliferation. B: HE, $\times 400$: tumor cells are arranged in nests or Zellballen and separated from sinusoidal capillaries. The tumor cells are polygonal and medium-sized, with granular amphiphilic cytoplasm and regular nuclei.

In 59.57% of cases, immunohistochemical confirmation was performed. Chromogranin (100%) and synaptophysin (96%) were positive (**Figure 3**). S100 expression was noted in 62.5% of cases. SDHB immunohistochemistry was not performed.

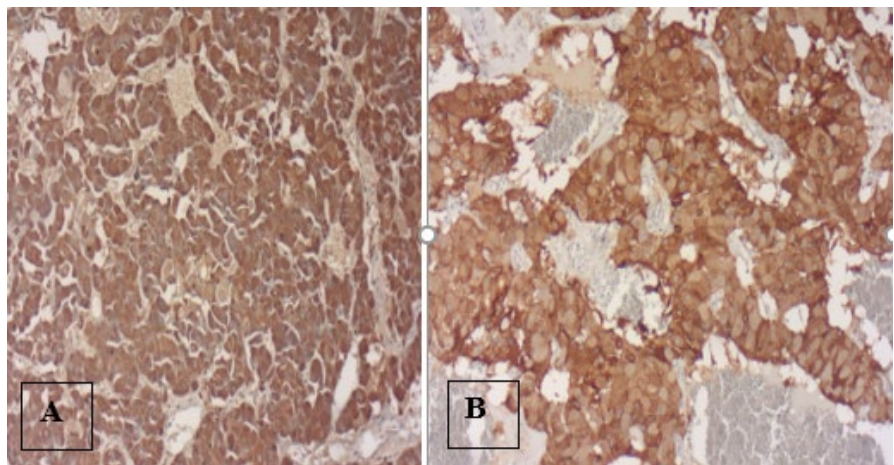


Figure 3. Immunohistochemical profile of pheochromocytoma. A: $\times 100$, anti-chromogranin antibody (strong and diffuse cytoplasmic staining of tumor cells). B: $\times 400$, anti-synaptophysin antibody (strong and diffuse cytoplasmic staining of tumor cells).

The PASS score was specified in 31.91% of cases. This score ranged from 0 to 14. Nuclear pleomorphism was noted in 34.04%, capsular invasion (14.89%), vascular invasion (12.76%), adipose invasion (6.38%), mitoses greater than 3/10CFG ($\times 400$) (25.53%) and atypical mitoses (4.25%). The tumor was potentially non-aggressive (65.96%) or potentially aggressive (34.04%) (**Figure 4**).

It was classified as pT1 (27.27%), pT2 (65.91%), and pT3 (6.82%). Renal hilar

(2.13%) and hepatic (2.13%) lymph node metastases were noted. The tumor was diagnosed at stage I (27.27%), stage II (63.64%), stage III (6.82%), and stage IV (2.27%). The data for follow-up was not available in the files.

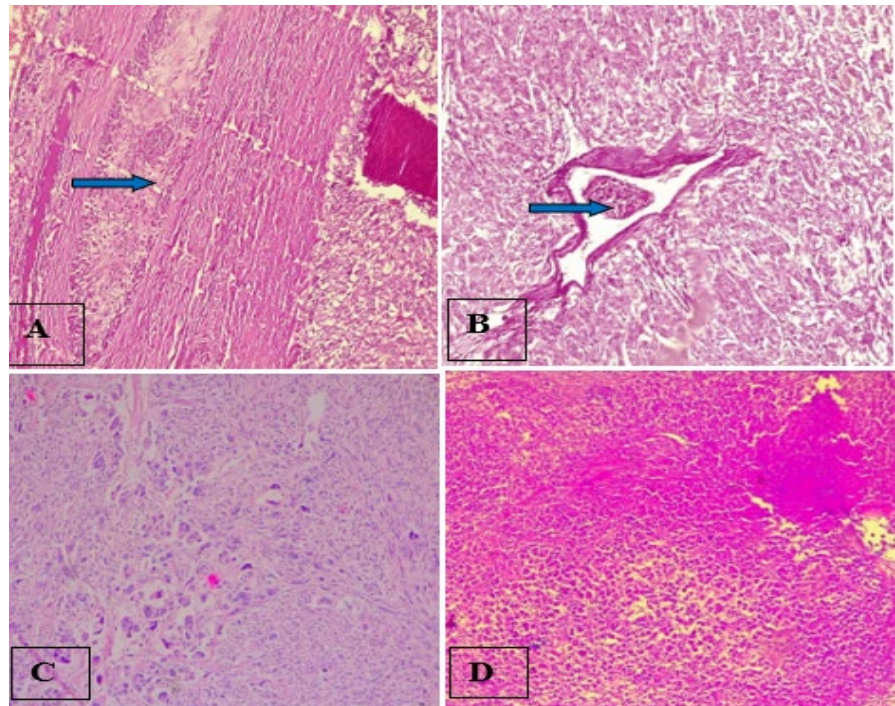


Figure 4. Histological images of an aggressive pheochromocytoma. A: HE, X100: focal capsular invasion (arrow). B: HE, X100: focal angioinvasion (arrow). C: HE, X100: Focal area of marked nuclear pleomorphism. D: HE, X100: Area of tumor necrosis.

4. Discussion

Pheochromocytoma is a relatively rare tumor. Our annual frequency was 1.52 cases, which is slightly higher than that found by Sagna *et al.* in Burkina Faso and Zantour *et al.* in Tunisia, which were 0.5 and 0.34 cases, respectively [4] [5]. In contrast, Zaher *et al.* in Morocco noted a frequency of 3.28 cases [6].

Females were the most represented gender, with a sex ratio of 0.68. Takongmo *et al.* in Cameroon and Tekaya *et al.* in Tunisia also found this female predominance, with sex ratios of 0.12 and 0.57, respectively [7] [8].

The average age of our patients was 48.06 years. This is slightly higher than that reported by Mekni *et al.* in Tunisia and Koama *et al.* in Burkina Faso, who found average ages of 47 and 42 years, respectively [9] [10]. Tekaya *et al.* in Tunisia found a slightly higher result of 51.2 years [8].

The tumor location was unilateral only and frequently in the left adrenal gland in 56.52% of cases. In contrast, Bettaiebi *et al.* in Tunisia found a clear predominance in the right adrenal gland in 80% of cases [11]. This contrasts with Rabii *et al.* in France, who found no predominance of laterality [12]. Nel *et al.* in South Africa found bilateral involvement in 5% of cases [13]. These results confirm the absence of a predilection site.

There was a personal history of paraganglioma (6.38%) and medullary thyroid carcinoma (4.26%). These cases could fall within the scope of familial pheochromocytoma. However, confirmation would require cytogenetic or immunohistochemical testing. This result is consistent with data in the literature, according to which 30% of pheochromocytomas are hereditary [14].

Abdominal mass was the main symptom in 57.50% of cases. In contrast, Proye *et al.* in France found this symptom in 10.2% of cases [15].

This predominance could be explained by delayed diagnosis when the tumor causes a mass or pain. High blood pressure was noted in 37.50% of cases. This result is lower than that of Baguet *et al.* in France [16]. Ménard's triad was noted in 27.50% of cases. This result is significantly lower than that of Jandou *et al.* in Morocco, who found a result of 75% [17]. It is higher than the 10% found by Kopetschke *et al.* in Germany [18]. In sub-Saharan Africa, studies have shown a high frequency of hypertension and Ménard's triad [4] [19] [20]. This variability in symptoms could be explained by the variability of the study settings and the non-exhaustiveness of the symptoms reported in the pathological examination reports.

These were exclusively total adrenalectomy specimens, 6.38% of which were enlarged to the kidney. This exclusivity could be explained by the fact that biopsy is contraindicated, due to the risk of causing capsular rupture and tumor dissemination. In cases of extension to the kidney, with which the adrenal gland has close connections, adrenalectomy is extended to the kidney [21] [22].

The average tumor size was 6.92 cm in our series. This result is similar to that of Djefal *et al.* in France, which was 6 cm [23]. It is slightly lower than that of Holland *et al.* in Canada, who found a result of 4.5 cm [21].

The tumor was often well-defined (91.67%), encapsulated (84.85%), grayish (53.85%) with hemorrhagic changes (65.97%). These results are consistent with the data in the literature [3] [14]. The circumscribed and encapsulated appearance could be related to the predominance of non-aggressive cases.

There was a predominance of trabecular (93.62%) and alveolar (53.19%) architecture. The stroma was endocrine in 100% of cases. These features are characteristic of pheochromocytoma, in line with its neuroendocrine nature [14] [24]. There was a 4.25% incidence of composite ganglioneuroma-type tumors. Composite tumors are rare and dominated by the ganglioneuroma component [3] [14].

Immunohistochemical confirmation was performed in only 59.57% of cases. This could be explained by the often typical histological appearance and the unavailability of immunohistochemistry in some laboratories.

Chromogranin A, synaptophysin, and S100 were expressed in 100%, 96%, and 62.5% of cases, respectively. Chromogranin A is the most specific and highly sensitive marker. However, it is recommended to combine it with at least one other neuroendocrine marker [25]. Immunohistochemistry is also used as a genetic screening and prognostic tool. SDHB immunostaining can be performed to identify a common germline mutation of the SDHx gene resulting in a lack of expression. Loss of S100 and SDHB expression is often associated with more aggressive and metastatic tumors [26].

The PASS score was specified in only 31.91% of cases in the conclusion of the pathology report and evaluated for the rest. This low frequency could be explained by the absence of this score before 2002 [27]. The most frequently found PASS characteristics were nuclear pleomorphism (34.04%), necrosis (29.79%), nuclear hyperchromatic (23.40%), capsular invasion (14.89%), and vascular invasion (12.76%). This predominance has also been reported by some authors [27] [28].

Pheochromocytoma was potentially non-aggressive in 65.96%, potentially aggressive in 34.04%, metastatic in 4.25%, and often diagnosed at stage II in 63.64%. These results are consistent with data in the literature, which show that potentially non-aggressive forms are the most common, with metastatic forms rarely occurring in 10 to 15% of cases [14] [27]. This early diagnosis could be explained by the accessibility of diagnostic tools and the frequently non-aggressive nature of the tumor. However, the very low frequency of metastatic forms could be explained by the lack of follow-up of aggressive cases.

5. Conclusion

Pheochromocytoma is rare in central Tunisia. It frequently affects women. It is most often symptomatic, non-aggressive, and diagnosed at a fairly early stage. Anatomopathological study is of paramount importance for histological confirmation, prognosis assessment, and genetic characterization for better patient management. Studies on the evolutionary and genetic aspects are also necessary.

Authors' Contributions

Rahim Ben Haddaoui Sedogo, Aïda Sandrine Ouedraogo, Albadia Sidibé, Ezékéel Judicaël Bocovo, Sidd-Bé Hamidou Yoni, Domèbegnevouo Rolande Nabewle Somé: data collection and participation in writing the article. Franck Auguste Hermann Adémayali Ido, Aimé Sosthène Ouedraogo, Moncef Mokni: critical review and validation of the article. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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