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The Place of the Department of Pathological Anatomy of the CHU Ibn Rochd Casablanca in the Diagnosis and Classification of Bronchopulmonary Cancer

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Abstract:-

➢ ***Introduction:***

Bronchopulmonary cancers (CBP) represent the leading cause of death in men worldwide. In this study, we present the epidemiological, histopathological, and immunohistochemical characteristics of CBP diagnosed in Moroccan lung cancer patients.

➢ ***Methods:***

We conducted a cross-sectional study during the year 2018. We used a data sheet for collecting clinical, histological, and immunohistochemical data of CBP patients. Descriptive statistical analysis was performed to determine frequencies and percentages. Bivariate analysis was used to examine the association between the dependent variable (histological type) and independent variables (age and gender).

➢ ***Results:***

In 2018, we analyzed the anatomopathological reports of 246 CBP patients, with an average age of 61.3 years and a gender ratio of 2.72. Adenocarcinomas (ADC) were the most common, accounting for 54.5% of cases. The TNM classification of operated cases showed that tumor sizes T2, T3, and T4 represented 20%, 57%, and 23%, with N0 at 40%, N1 at 33%, and N2 at 27%. Secondary tumors accounted for 10% of cases, with 46% originating from the breast. Immunohistochemically, TTF-1 expression was found in 89% of ADC cases, anti-p63 antibody expression was positive in 100% of squamous cell carcinoma cases. For neuroendocrine carcinoma cases, synaptophysin expression and chromogranin A had positivity rates of 100% and 60%, respectively. Bivariate analysis did not show any significant association between histological types and age or gender.

➢ ***Conclusion:***

We concluded that this series allows for the analysis of the profile of CBP cases diagnosed in a major lung cancer treatment center in Morocco. The predominance of adenocarcinoma tumors in the profile should caution against hasty conclusions, with the systematic testing of TTF-1 and anatomoclinical correlation before determining the primary tumor. Diagnosis remains delayed in our context due to the advanced stages that continue to prevail.

Keywords:- *Bronchopulmonary Cancer, Epidemiology, Histopathology, Immunohistochemistry.*

I. INTRODUCTION

Despite advances in the field of oncology diagnostics and therapeutic management, lung cancer remains a major public health problem, being the leading cause of death in men worldwide. In Morocco, lung cancer is considered the second most common cancer after breast cancer, with a prevalence of 12.4% for both sexes, which can reach 22.3% in men, followed by prostate and colorectal cancer (Globocan 2020). There are two main types of lung cancer: non-small cell lung cancers (NSCLC), which account for approximately 80%, and small cell lung cancers (SCLC), which make up about 20% (Kanitkar A and al 2018). As for the histological types of NSCLC, they are primarily represented by adenocarcinoma (ADC) and squamous cell carcinoma (SCC) (Glatzel-Plucinska et 2018).

Thanks to the new insights provided by global multidisciplinary studies on bronchopulmonary cancers (BPC) and the new WHO classification (2015 Classification), anatomopathological examination is crucial in the diagnosis and classification, and subsequently in the treatment of this disease. However, the absence of both a national lung cancer registry and sufficient data on this situation necessitates epidemiological and anatomopathological studies of this pathology.

Hence the objective of our study is to establish the clinical and anatomopathological profiles of cases of BPC diagnosed at the Pathology Department of the Ibn Rochd University Hospital in Casablanca.

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II. METHODS

➢ *Study Design:*

This is a cross-sectional study based on the anatomopathological reports of patients with BPC.

➢ *Study Setting and Population:*

Our study was conducted at the pathology laboratory of the Ibn Rochd University Hospital in Casablanca, a major center for the diagnosis of tumor pathologies in Morocco, with 246 medical records of Moroccan patients with BPC during the year 2018 (pre-COVID-19). All confirmed cases of BPC were eligible for inclusion in the study.

➢ *Variables:*

The studied variables included age, gender, nature, site of sampling, histopathological characteristics, and immunohistochemical features of the tumor. The independent variables were age and gender, while the dependent variable was histological type. The diagnosis of anatomopathological bronchopulmonary carcinoma (CBP) is based on:

➢ *Histopathological Examination:*

It was performed on biopsies and surgical specimens involving the following steps: tissue fixation in 10% formalin, embedding in paraffin, cutting thin sections of 4-micron thickness, mounting between glass slides and coverslips, and standard staining with hematoxylin and eosin (H&E). Non-small cell lung carcinomas (NSCLC) were diagnosed as squamous cell carcinoma (SCC) when keratin pearls and/or intercellular bridges were present. Adenocarcinoma (ADC) was considered when there was evidence of glandular differentiation and/or intracellular mucin vacuoles. Other cases with a solid growth pattern or lacking defined differentiation were classified as nonspecific non-small cell lung carcinoma (NSCLC-NOS).

➢ *Immunohistochemical Examination (IHC):*

The anatomopathological diagnostic process for NSCLC differentiates ADC from SCC and NSCLC-NOS (Référentiels en oncologie thoracique 2019).

Meanwhile, for the diagnosis of pulmonary neuroendocrine tumors (NETs), it requires positivity for at least one of the validated neuroendocrine markers commonly used (chromogranin, synaptophysin, CD56) (Travis WD and al 2004). Immunohistochemical analysis in our laboratory was carried out using the DAKO Autostainer Link48 automatic system (Dako). Antigen visualization was accomplished with the EnVision FLEX kit (Dako) and counterstained with Mayer's hematoxylin. Histopathological evaluation and pathological staging were performed according to the criteria recommended by the World Health Organization (WHO, 2015) (Classification OMS 2015). Immunohistochemical expression of diagnostic biomarkers was assessed using monoclonal antibodies: anti-TTF1 (Thyroid Transcription Factor 1) (Clone: 8G7G3/1), anti-P63 (Clone: DAK-P63), anti-Napsine (Clone: KCG/1), anti-synaptophysine (Syn) (Clone: DAK-SYNAP), anti-Chromogranine A (Chr A) (Clone: polyclonal antibody), anti-CD56 (Cluster of Differentiation 56) (Clone: 123C3), anti-CK7 (Cytokeratin 7) (Clone: OV-TL), and anti-CKAE1/AE3 (Clone: AE1/AE3). The tumor expression of the main diagnostic biomarkers for CBP is interpreted as shown in Figure 1.

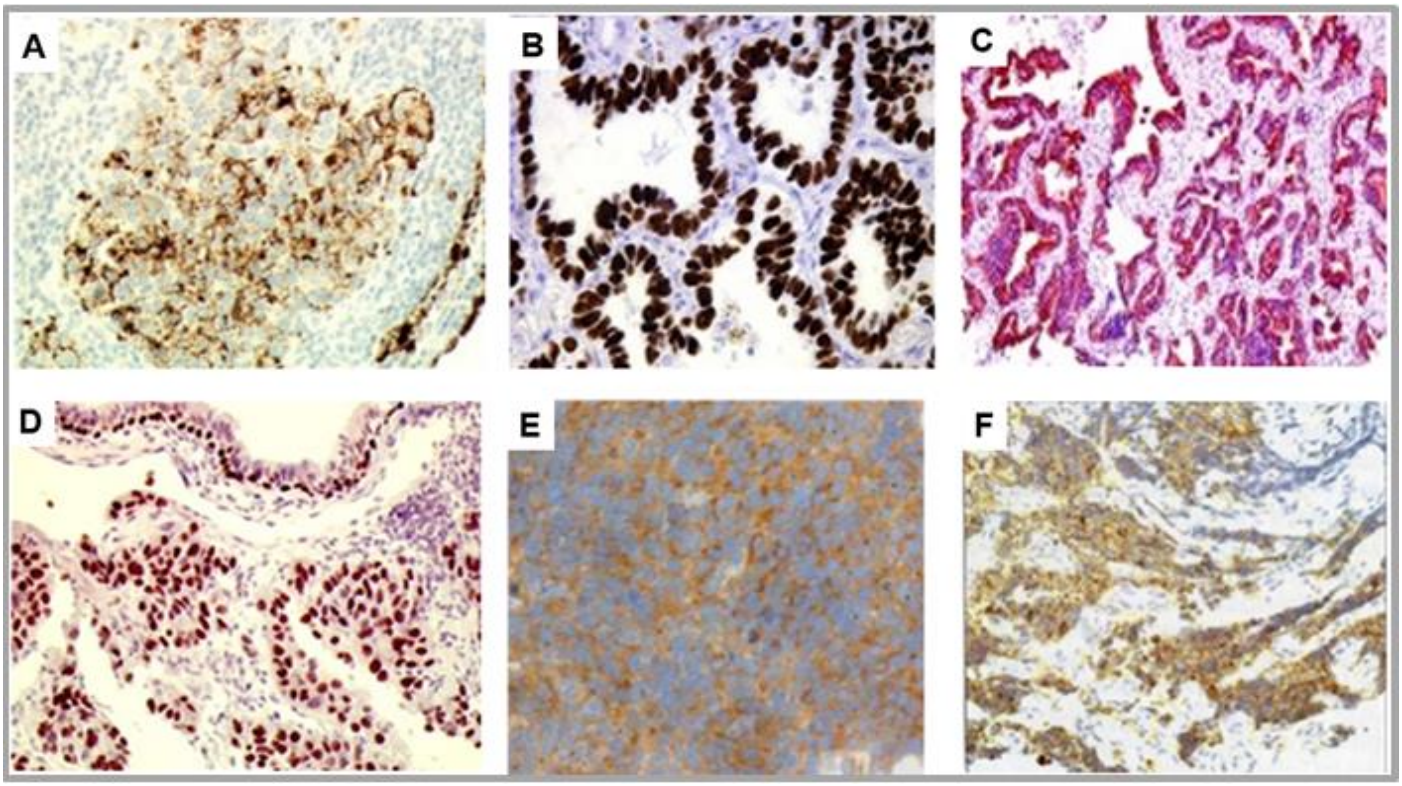

Fig 1 IHC Expression of Antibodies on Tumor Cells
A: Napsin A; B: TTF-1; C: CK7; D: P63; E: Synaptophysin; F: Chromogranin

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➢ *Data Resource and Measurement:*

- Data Collection Tool:

A data sheet for collecting clinical, histological, and immunohistochemical data of patients with CBP has been designed.

- Data Collection:

In our study, we collected clinical and pathological data from 246 cases of CBP during the year 2018, "a pre-COVID year," from the histopathological reports of patients confirmed to have CBP through histopathological and immunohistochemical examinations.

➢ *Data Analysis:*

Descriptive analysis of quantitative variables was performed using the SPSS software to calculate the mean and median for the variable "age," as well as the percentages of other variables. Additionally, we used Pearson correlation and one-way ANOVA to study the association between histological types, age, and sex. A P-value less than 0.05 is considered statistically significant.

➢ *Ethical Considerations:*

Our study was approved by the ethics committee of our institution at CHU Ibn Rochd in Casablanca and conducted in accordance with the Helsinki Declaration recommendations.

III. RESULTS

➢ *Clinical-Pathological Characteristics of Patients*

- *Socio-Demographic Analysis:*

In 2018, we analyzed histopathological reports from 246 CBP patients. The median age of the patients (N=246) was 62 years, with an average age of 61.3 (± 9.2) ranging from 28 to 94 years. Among them, 54% (N=132) were older than 61.3 years, and the gender ratio was 2.72.

- *Descriptive Analysis:*

Regarding the type of sampling, 88% (N=216) were biopsies. As for the site of sampling, 48% were taken from the lung, 34% from the bronchi, and 16% from the pleura.

The characterization of tumors revealed the following histological types: 134 cases of ADC, accounting for 54.5%; 30 cases of SCC, accounting for 12%; 26 cases of secondary tumors (TS), accounting for 10.5%; 24 cases of NET, accounting for 10%; and 22 cases of SCLC, accounting for 9.5%.

The TNM classification of the 30 operated cases only concerned the tumor size (T) and the number and location of affected lymph nodes (N). T2, T3, and T4 tumors represented 44%, 38%, and 18%, respectively, with N0 at 60%, N1 at 27%, and N2 at 10%.

Secondary tumors (26 cases) accounted for 10.5% of cases, with 46% of them originating from the breast, 27% from the stomach, and 15% from the prostate.

All the aforementioned results are summarized in the summary table (Table 1).

Table 1 General Patient Characteristics

Variables	Number of patients	(%)
Age (years)		
Median Rank	62 [28-94]	
Mean Standard Deviation	61,3 [9,2]	
≤ 61,3	114	46
> 61,3	132	54
Gendre		
Men	180	73
Women	66	27
Sexe ratio	2,73	
Histological type		
Adenocarcinoma	134	54,5
Squamous cell carcinoma	30	12,1
Secondary tumors	26	10,5
neuroendocrine tumor	24	10
Small cell lung cancer	22	9
Site of sampling		
Lung	118	48
Bronchus	85	35
Pleura	38	15
Trachea	3	1
Mediastinum	2	1
Stage of disease		
T2, T3, T4	6, 17, 7	20, 57, 23
N0, N1, N2	12, 10, 8	40, 33, 27

The architecture of ADCs revealed the following types: 47% acinar, 28.6% solid, 9.5% papillary, 9.5% mucinous, and 4.8% lipid-rich (Figure 2).

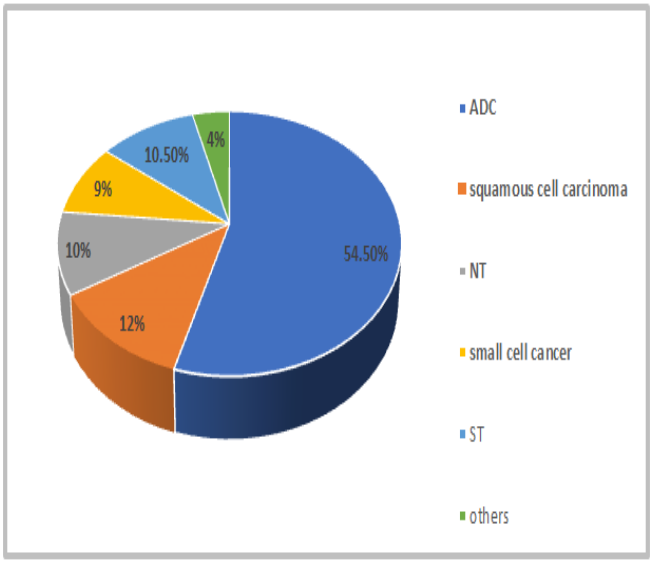

Fig 2 Distribution of Histological Types of Lung Cancer
ADC: Adenocarcinoma; NT: Neuroendocrine Tumors; ST: Secondary Tumors.

Immunohistochemically, TTF-1 expression was found in 89% of ADCs, and the expression of anti-p63 or anti-p40 antibodies was positive in 100% of SCC cases.

As for NET cases, synaptophysin and chromogranin A expression had positivity rates of 100% and 60%, respectively (Table 2).

Table 2 Antibodies positivity rate in IHC

Histological type	Antibodies (%)						
	TTF1	P63	Ck7	CD56	Syn	Chr	CK AE1/AE3
ADC	89	7	80	0	0	O	NF
Squ cel car	6	100	NF	NF	NF	NF	NF
Neur tum	NF	NF	NF	91	100	60	100

ADC: Adenocarcinoma; Squ cel car: squamous cell carcinoma; Neur tum: Neuroendocrine Tumors.
NF: Not Done, TTF1: Thyroid Transcription Factor 1, Chr A: Chromogranin A, CD56: Cluster of Differentiation 56, CK7: Cytokeratin 7.

- *Bivariate Analysis of Histological Types with Age and Gender:*

In our study, no statistically significant differences were observed between histological types, age, and gender. Table 3 represents the results of the bivariate analysis of histological types with age and gender.

Table 3 represents the results of the bivariate analysis of histological types with age and gender.

Variables N (%)	Total (N=246)	ADC	SCC	ST	NT	SCLC	Others	P value
Age (years)								0.442
≤ 61.3	112 (47)	65 (58)	12 (10.8)	12 (10.8)	10 (8.8)	9 (8)	4(3.6)	
> 61.3	134 (53)	69 (51.5)	18 (13.4)	14 (10.5)	14 (10.5)	13 (9.7)	6 (4.4)	
Gender								0.435
Men	179(72.7)	98(54.7)	22 (12.3)	19 (10.6)	16 (8.9)	18 (10)	6 (3.4)	
Women	67(27.2)	36 (53.7)	8 (11.9)	7 (10.5)	8 (11.9)	4 (6)	4 (6)	

ADC:Adenocarcinoma; SCC: squamous cell carcinoma; NT: Neuroendocrine Tumors; ST: Secondary Tumors; SCLC: Small Cell Lung Cancer.

IV. DISCUSSION

In our study, there were 246 diagnosed cases in the year 2018. This figure remains high compared to most studies available in Morocco and Africa. A Senegalese study reported 77 cases of CBP over 8 years (Niang A and al 2018), and another Egyptian series reported 255 cases of CBP over 4 years (Omar A and al 2017). In contrast, a French study recorded 7,051 cases in one year (Coëtmeur D and al 2010). This reflects the reality of CBP cases diagnosed in our Pathological Anatomy Laboratory, which serves as a major center for lung cancer management in Morocco. Hence, the need to strengthen preventive measures and early diagnosis to reduce the incidence of this pathology.

The average age of the subjects is 61.3 years, with a range from 28 to 94 years. It is roughly consistent with the study by Ben Amar and al. in Tunisia (2005-2010) (Ben Amar A and al 2012) and that of Bourkoua and al. (2017-2018) in Algeria (Bourekoua W and al 2019). Patients aged 61.3 years and older make up more than half of the cases. These data confirm that bronchopulmonary cancer primarily affects the elderly (Ndiaye and al 2015).

The distribution of cases by gender shows a male predominance in 73% of cases, with a sex ratio of 2.72. These numbers are in line with the literature (Elkhattabi and al 2018).

The nature of the samples was biopsies, accounting for 88% of the samples. This figure is close to the literature (94.59%) (Ketfi A and al 2017). The rarity of surgical specimens could be explained by the fact that patients with CBP are often diagnosed at an inoperable stage.

In our series, the most common histological type of CBP was ADC, accounting for 54%, followed by SCC (12%) and NEC (10%). Our results are in line with the literature (Ketfi A and al 2017, Rajeb and al 2020, Cadelis and al 2013). Table 4 shows the distribution of histological types of CBP in different studies.

Table 4 Distribution of histological types of CBP in various studies

Series	ADC	SCC	NT	SCLC	Others
Omar and al [8]	51,8	22,7	18,4	------	------
Niang and al [7]	44,1	27,3	11,7	------	------
Elkhattabi and al [13]	66%	31%	------	------	------
Ketfi and al [15]	53,7 %	27,1 %	11,7	------	------
Rajeb and al 2018 [16]	50%	29%	------	20%	------
Cadelis and al [17]	43%	24%	------	7,5%	------
Notre série	54,5%	12%	10%	9%	4%

ADC: Adenocarcinoma, SCC: Squamous Cell Carcinoma, NT: Neuroendocrine Tumors, SCLC: Small Cell Lung Cancer, ST: Secondary Tumors

Regarding the distribution of ADC subtypes, acinar architecture was the most frequent histological subtype at 47.6% of cases, followed by solid architecture ADC at 28.6%, and papillary ADC at 9.5%. These results are consistent with the literature (Thiberville and al 2004).

Our results for tumor size T2, T3, and T4 are similar to the findings of the study by Mansuet-Lupo and al. (Mansuet and al 2014) , especially in terms of T2 and T4. In contrast to the results of Julio Sánchez's study (Julio and al 2014), he showed that 46% of cases were classified as T4 and 21% as T3, as opposed to 33% in T1 and T2. As for the affected lymph nodes, the study by J. Guinde and al is similar to our results concerning pN2 (Guinde and al 2020).

The statistical analysis did not show any significant association between the variables under study, the histological types with age and gender, based on age (P=0.442) and gender (P=0.435). A study by A. Aboussad and al (Aboussad and al 2010) revealed that men have a significantly higher risk of lung cancer compared to women. This elevated male risk is primarily due to smoking, which is the major cause of lung cancer, and to a lesser extent, occupational and environmental exposure to carcinogenic substances, which is more prevalent in men.

Several studies have been conducted to establish a diagnostic algorithm for CBP, based on a panel of specific antibodies for each entity. The diagnostic approach followed the new recommendations of the 2015 WHO histological classification of CBP. Immunohistochemistry was used for all cases where morphology did not allow for a formal conclusion, especially TTF1 and Napsin A, p63, or p40 for distinguishing between ADC and CE, and the markers CD56, chromogranin A, and synaptophysine for NEN (Lantuejoul and al 2016). In the present study, the results show a positive expression percentage of TTF1 and p63 or p40 antibodies similar to the studies of Halla Vidarsdollir and al (Vidarsdollir and al 2019) and S.Mukhopadhyay and al (Mukhopadhyay and al 2011), which respectively had a positivity expression for TTF1 of 90% and 80% for ADC, and a positivity expression for p63 of 97% and 100% for CE. Regarding the diagnosis of neuroendocrine carcinoma, neuroendocrine markers, Chromogranin A, and Synaptophysine are only used in cases of morphological suspicion of NEN (Julio and al 2014, William and al 2016). In the case of a single marker expressed, this marker must show positivity in ≥ 50% of the examined tumor cells (ONCOLOGIK and al 2021). In our study, Chromogranin A and Synaptophysine have positivity of 100% and 60% respectively. Our results are consistent with those published by Annamaria C and al (Annamaria and al 2014).

The limitations of our study include certain clinicopathological data such as smoking status, performance status (PS), and disease stage. Furthermore, the molecular profile of the recruited patients. Additionally, the prospects of our study involve evaluating the molecular profile of recruited patients to personalize therapeutic management.

V. CONCLUSION

This series allows for the analysis of the profile of CBP cases diagnosed in a major lung cancer treatment center in Morocco. The relatively common occurrence of adenocarcinoma should encourage caution, with systematic testing of TTF-1 and anatomoclinical correlation before concluding a primary tumor. The diagnosis remains late in our context due to the prevailing advanced stages. It is necessary to strengthen primary prevention based on anti-smoking efforts and to study the risk factors and molecular alterations of this type of cancer for better management.

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