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Molecular Characterization of Gastrointestinal Stromal Tumors (Gist) and Contribution of Immunohistochemistry in Congolese from Kinshasa

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Abstract

Introduction: The differentiation of digestive tumors very often requires the use of techniques currently not widely in use in the Democratic Republic of Congo (DRC), such as immunohistochemistry. This is perfectly verified for GISTs whose precise, or at least highly certain, diagnosis can only be made using immunohistochemical markers. This underuse of these techniques due to lack of equipment and human skills explains the limited epidemiological data available to date, thus leading to untargeted and too often late treatment of patients. **Research question**: What contribution can immunohistochemical markers make to the diagnosis of digestive tract tumours? **Objective**: Discuss the contribution of immunohistochemical markers in the diagnosis of GIST and provide basic data on the epidemiology of these nosological entities in Kinshasa. **Methodology**: This was a retrospective study carried out at the LEBOMA private anatomy and pathological cytology centre. The main inclusion criterion was any digestive tract block or slide whose diagnosis of GIST had been requalified after review by at least 2 pathologists. An immunohistochemical study was performed using an automated technique (with a Ventana XT machine) using a panel of antibodies: CD-117 and DOG-1 which are listed in the literature as strongly correlated with the occurrence of GIST, all slides were made at Hj Hospital using an OLYMPUS BX41 co-observation microscope. **Results**: Of 601 cases of digestive tumors recorded during the concerned period, 32 (5.32%) concerned GIST. This prevalence was con-

firmed by our immunohistochemical results where the expression of CD117 and that of DOG-1 were positive in 90.6% and 100% of cases which prevalence is high compared with the worldwide prevalence according to the literature, respectively. The distribution of the patients concerned was made with a sex ratio of 1.6 women/men with a median age of 53 years. Most cases (81%) had a gastric location and were fusiform GISTs. **Conclusion**: Gastrointestinal stromal tumours, although rare and underestimated, account for 5.32% of cases in the DRC. This is a considerable and high prevalence compared with the world average. To the best of our knowledge, no studies have been carried out on these aspects in the DRC, which explains the importance of this study. The results of this research demonstrated the contribution of these 2 markers as specific and effective biomarkers for optimal and differential diagnosis in GIST. In view of the above, it is therefore more than necessary to popularise the use of these biomarkers in order to contribute effectively to improving the overall management of gastrointestinal tumours by improving their identification.

Keywords

Digestive Tumors, GIST, Immunohistochemistry,CD117, DOG-1

1. Introduction

Gastrointestinal stromal tumors (GIST) are considered rare and represent approximately 1% of digestive tumors [1] [2]. However, these are the most common mesenchymal tumors of the digestive tract (80%) [3]. The exact incidence has long been underestimated since these tumors were initially not clearly identified as a separate nosological identity. The symptoms caused by gastrointestinal stromal tumours are mostly non-specific, even if some of them sometimes give indications as to their origins. Nevertheless, in the majority of cases according to the various studies, digestive bleeding remains the most frequently revealing symptom, followed by abdominal pain, then the discovery of an abdominal mass and the lesion discovered incidentally in some patients [2]. In addition, some GIST are asymptomatic then undiagnosed [4], and most studies carried out are retrospective in nature. Immunohistochemical studies make it possible to confirm the diagnosis and to exclude other tumors such as leiomyomas or schwannoma which could be confused histologically with stromal tumors. The reference marker is the CD117 protein, a transmembrane receptor encoded by the c-kit proto-oncogene, which is positive in approximately 95% of GISTs [5] [6] [7] [8]. Other markers are also described to refine the diagnosis, notably DOG1, particularly in the case of CD-117 negativity [9]. CD34 [10], Desmin [11] and PDGFRA [12] [13] can also be cited. Søreide *et al.* conducted a review of the global GIST epidemic identifying 29 studies with more than 13,550 patients from 19 different countries. It appears that no African study could be identified. Furthermore, in the Democratic Republic of Congo, to our knowledge, no study focusing on these immunohistochemical

aspects has ever been carried out. This is why it seemed useful to us to carry out this work to, on the one hand, draw up the histopathological profile of GISTs in Kinshasa and on the other hand, discuss the contribution of two immunohistochemical markers: CD117 and DOG-1.

2. Materials and Methods

We identified, in a private anatomopathological laboratory in the city of Kinshasa, all medical records reporting a digestive tumor, collected during the period from 2015 to 2022. We then selected among them reports suspecting GISTs and for which samples were available, of sufficient material and correctly preserved.

Tissue blocks were subjected to sectioning (3 - 5 µ sections) and staining (with HE), and finally, they were observed under a light microscope. Slides were re-examined histologically by two specialized pathologists; in case of discrepancies a third advice was needed. The histological type and the biological behaviour were assessed.

Immunohistochemistry was carried out within HJ Hospital pathology lab, using a fully automated VENTANA ULTRA (VENTANA Medical Systems; Roche Group, Tucson, AZ, USA) using anti-CD117 (EP10) rabbit monoclonal primary antibody and DOG1 (SP31) rabbit monoclonal primary antibody, with the Optiview DAB IHC detection and Optiview amplification kits. Furthermore, each sample was stained with a matched rabbit monoclonal negative control immunoglobulin antibody. The immunostains were evaluated by three well-trained independent pathologists and the slides were examined with a light microscope at a final magnification of ×400.

Ethical Considerations

This study has received the ethical approbation of the institutional committee of the Faculty of Medicine, University of Kinshasa. Confidentiality and anonymity were fully respected.

3. Results

3.1. Frequency

601 medical reports concerning digestive tumors were collected for the study period (2015-2022) among which 32 (5.32%) alluded to GISTs where females predominated (63%), with a sex ratio of 1.6/1. The median age was 57 (range 23 - 68) (View Table 1).

Table 1. AGE.

Age group GIST	Female	Male	Total
23 - 45 years old	6 (19%)	6 (19%)	12 (38%)
46 - 68 years old	14 (44%)	6 (19%)	20 (63%)
Total	20 (63%)	12 (38%)	32 (100%)

The distribution of study subjects according to age groups shown in this figure shows that the majority of patients were in the age group of 46 to 68 years, or 63%, the median age was 57 years. , the youngest were 23 years old and the oldest were 68 years old.

3.2. Pathological Features

The initial orientation diagnosis was made mainly from biopsy (75%) then from operative specimens (25%) (View Table 2). Gastric and colon localization accounted, respectively, for 81% and 19% (View Figure 1). Histologically, spindle-shaped component predominated (81.25%), followed by the mixed (12.5%) and the epithelioid ones (6.25%).

In our series, the means of diagnostic confirmation were: biopsy which represented 75%, *i.e.* 50% in female subjects and 25% in male subjects.

3.3. Immunohistochemical Profile

CD117 and DOG-1 expression was detected, respectively in 90.6% and 100% of histologically suspected GIST (View Figure 2).

Table 2. Type of sampling.

Type of gist sample	Female	Male	Total
Biopsy	16 (50%)	8 (25%)	24 (75%)
Operating room	4 (13%)	4 (13%)	8 (25%)
Grand total	**20 (63%)**	**12 (38%)**	**32 (100%)**

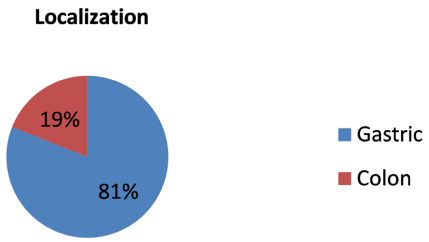

Figure 1. Frequent location of GISTs.

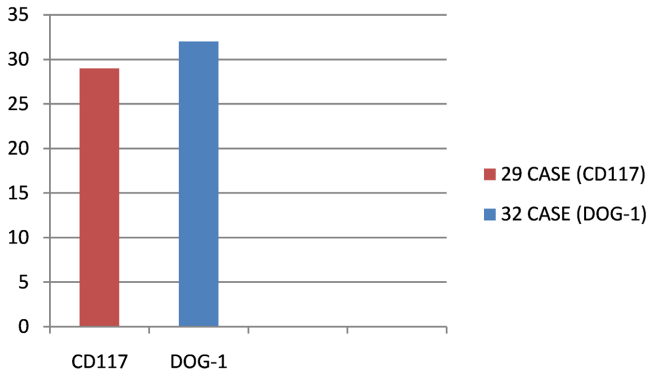

Figure 2. CD117 and DOG-1 expression.

In our series, analysis of CD117 expression was done in all cases (32). It came back positive in 29 cases. While the analysis of DOG-1 expression was done in all cases (32) and it was positive in all cases.

4. Discussion

Gastrointestinal stromal tumors are the most common mesenchymal tumors but are quite rare considering the overall digestive tract tumors. In the present work, we noticed a relative frequency of 5%, which is not that different from the values (1%) reported by Gheorghe M *et al*. [13]. GIST usually occurs in people over 50 years old [14] [15]. Our results are in accordance with this as the median age calculated was of 57 years. It appears that no gender predominance exists for GIST [16] but our results showed a slightly female predilection. This seems to have no particular significance. The main localization found, as previously reported everywhere [17] [18] [19], was gastric (81%) immediately followed by the colon (19%). DeMatteo RP *et al*. reported comparable results (15%) for colorectal localization [15]. Although GIST can appear anywhere in the digestive tract, no other localization was noticed in our sample.

Microscopically, the spindle-shaped type was observed in just over 80% of cases. This corresponds to what is everywhere described in the literature [11] [17] [20]. However, we found more mixed types than epithelioid ones, which diverges from what is usually described. Further studies will determine whether this trend is an isolated fact or an epidemiological feature of our settings.

Nowadays, a presumptive diagnosis of GIST can be made relatively easily due to their better definitions and characteristic morphology. This fact is illustrated in our results where all the cases were correctly histologically suspected of being GIST. However, the situation was quite different a decade ago, when the histogenesis of GIST was less well known. As an illustration, in a similar study involving samples collected between 1983 and 2000 [15], only 28% could be correctly identified as GIST on a histological basis. In fact, for a long period GISTs were considered of smooth-muscle origin [21] instead of the differentiated stromal cell origin now generally accepted [6]. Thus, all our samples were positive for DOG-1 but a little less (90.6%) for CD117. DOG-1 expression was positive in all our CD-117 negative cases. This is in line with what the literature reports [22] [23]. Liegl *et al*. stated that DOG-1 shows higher sensitivity than KIT in the diagnosis of GIST [9]. However, some studies have reported data where CD117 expression is higher than DOG-1 [24] [25]. This discrepancy might be explained by the clinicopathological differences between the sample groups. But generally, GISTs are known to be immunohistochemically positive for CD117 and DOG-1 in more than 80% of cases.

5. Conclusion

Advances in molecular biology have allowed a better understanding of certain cancer pathologies such as GISTs and therefore a better diagnostic and thera-

peutic approach. However, these techniques are still underused in the DRC due to the high cost, availability of equipment and reagents and trained personnel. We report here, to our better knowledge, the first work involving DOG-1 and CD-117 expression in DR Congo, thus providing baseline data for further research in GIST.

Credit Authorship Contribution Statement

Principal author: conception and drafting of the article.

OKUMADI Jérémie: participation in data collection and debate for approval of the version to be published.

Professor MVUMBI Dieudonné: revision of the main intellectual content and approval of the version to be published.

The other authors: Proofreading of the slides and participation in the debate for approval of the version to be published.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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