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Review Article

Clinical, and Diagnostic Characteristics of an Unsuspected Course of Urinary Tuberculosis: A Brief Report

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Abstract

Human Tuberculosis caused by *Mycobacterium tuberculosis* (MTb) remains a serious public health problem because of the high percentage of asymptomatic infection. Even worse, from this percentage, around 20% develop disseminated Tuberculosis involving the urinary tract. How to approach this?. A key issue is the accuracy and speediness of the diagnosis. In the present brief report, we described and pinpointed an unsuspected course of urinary Tuberculosis in an individual that presented signs not very characteristic of non pulmonary TB. The main symptoms were microhematuria, urinary incontinence, and urinary infections. To gain insight into the characterization of the clinical manifestations of the infectious disease, we pursued unconventional analysis assays, along with classic microbiological media tools. Molecular (microarrays, pattern of biomarkers) and serological reactivity (mycobacterial antigens detection) were determined in both blood and exudates. Remarkably, in the urinary diagnosis of Tuberculosis, these alternative tools could provide strong support and input to the clinics, especially in unsuspected cases.

Keywords: Urinary Tuberculosis; Hematuria; Urinary Contingency; BAAR; PCR; RT-PCR; Microarrays; Serological Reactivity

Introduction

Mycobacterium tuberculosis (MTb) is the etiological agent of Human Tuberculosis. It is a member of the Mycobacteriaceae family. Accordingly to the World Organization of Health (WHO), 1.7 million deaths and morbidity of 10.6 million. While most infected people remain asymptomatic (latent infection), only five percent develop the active disease [1,2]. Several factors favored the persistence and the global spread of MTb infection in developed countries as multi-drug drug-resistant strains (MDR), genetic susceptibility to mycobacterial infections, and other co-infections (HIV) [3-5].

Mycobacterium bovis Bacille-Calmette-Güerin (BCG) remains the only official vaccine worldwide effective against some forms of disseminated tuberculosis or tuberculosis associated with meningitis in children [6]. However, it fails to protect young and adult people [7].

Therefore, a much better understanding of the cellular and innate immune response protective antimycobacterial to facilitate the development of more efficacious vaccines against *Mycobacterium tuberculosis* as well as diagnostic or prognostic tests [8-12].

One form of extrapulmonary Tuberculosis that has been receiving attention is urinary tract Tuberculosis. It has become the third most common of disseminated Tuberculosis. Several studies have shown tha*t M. tuberculosis* can infect and disseminated toward other organs (urinary tract) [13-19]. In fact, from the 10 million of MTb infected people that develop pulmonary Tuberculosis, a higher of 20% develop genitourinary Tuberculosis affecting the anatomy and physiology of the urinary tract of men and women (UG-TB) [18-20]. Nowadays, IG-TB has become a serious and common health problem, especially in developed countries. The dormant state of the tubercle bacilli represents, thus, a "hot spot of infection" nowhere. The diagnostic of UG-TB is no easy task, since due precisely to the lack of clinic manifestations and the paucibacillary bacilli (1 to 9 BAAR X 100) [20,21]. The clinical manifestations of UG-TB are diverse. However, it is also true that co-morbility dity have also a role in the course and development of the infectious disease [17,19,22,23].

How early are UG-TB diagnoses in an asymptomatic patient? It is almost imposible without imagenology to detect any changes in the urinary tract renal parenchyma.

However, radiological changes become more evident in the renal parenchyma as the disease progress [19,22,24]. The UG-TB diagnostic is essential for good renal and urinary tract function and to avoid severe complications. Renal TB diagnosis is not always easy because *Mycobacterium tuberculosis* (MTb) detection is not always possible (1 to 9 BAAR x 100). In addition, antibiotic treatment, early kidney damages, and rare urological diseases can mask infectious diseases. Therefore, the timing in the diagnostic of UG-TB is fundamental [19,22,24-27].

Molecular techniques

Since polymerase chain reaction (PCR) discovering by Kary Mullis in 1983 becomes the molecular method for amplification to a small and large scale of DNA genomic sequence. More important outstanding were amplifying in samples with a low number of bacilli. The use of PCR in GUTB diagnostic was not the exception. Thus, van Vollenhoven in 1996 [28] validated the use of PCR from concentrated urine, resulting in faster than microbiological urine culture [16]. Despite this progress in UG-TB diagnosis, lesions by careful radiological examination in individuals of Africa and Europe [28,30]. Diagnosis of tuberculosis of renal and urinary tract using two methodologies. The identification of Koch acid-fast bacilli Ziehl-Nielsen stained on renal parenchyma biopsies and upper urinary tract [31]. Recent reports propose UG-TB diagnosis on three parameters: case history, pyuria, and radiological imaging. Other authors have suggested that histochemistry combined with molecular assays provide a more precise, accurate, and definitive UG-TB [18,27,31-36].

Microbiological techniques

One of the best biological diagnostic tests is the detection of the bacillus in clinical sample, be any fluids (urine, sputum) or tissue [23,36-39]. It is usually called as the gold microbiological test for UG-TB.

Imaging techniques

Imaging techniques have made it possible to localize sites and spread disease. Thus, determining the effect of the infectious lesion damage and associated pathology. In addition, using imaging equipment is also possible to have an alternative to obtain samples of the tissues or organ involved [23,38,40]. Furthermore, a set of integrated techniques yields good and faster results [41,42].

Biomarkers determination leads to a better understanding of the components that determine the disease spectrum, the reactivation of the dormant mycobacteria, and the progression of the disease [31,36,43-48]. Therefore, this tool represents a powerful and potential alternative to predict or define prognostic or diagnostic tests. Microarrays technologies have enabled biomarkers candidates determination to differentiate active versus latent Mycobacterium tuberculosis infection [47-48]. So far, this could potentiate the sensibility and specificity of diagnostic and prognostic

tests. However, microarrays still need to be scaled and developed for clinical purposes. Therefore, molecular methods that include amplification of mycobacterial DNA [34;49]; RT-PCR, GeneXpert MTB/RIF assay [27,35]. A series of methodologies can help in the diagnosis of urinary TB [23]. With the remarkable breakthroughs of the Next-Generation Sequencing (NGS) development, it would be expecting as a promising molecular tool for UG-TB diagnostic [37]. The challenge of this: be able to develop less invasive techniques, specific, sensitive diagnostic tests [26], and to have sufficient information to predict progression. Therefore, the goal for a successful UG-TB treatment outcome: an early, fast, and accurate diagnosis to avoid disease progression and kidney organ failure[23,26].

Clinical, Diagnostic characteristics

The clinical symptoms that an individual presented were incontinence, microhematuria, and recurrent infections in the urinary tract. Allergic to Ceftriaxone, penicillin, sulpha, and metoclopramide non-steroidal anti-inflammatory drugs (NSAD).Tolerant to amikacin and phosphocyl. Septumplasita SII in Torax. No systemic arterial hypertension (SAH). No Diabetes Mellitus type two) (DM2). No distioidismo (DT). Allergic to Ceftriaxone, penicillin, sulpha, and metoclopramide non-steroidal anti-inflammatory drugs (NSAD).Tolerant to amikacin and phosphocyl. No blood transfusion (BT), neither alcoholism nor smoking. Blood tests as a normal routine laboratory. Laboratory investigations were performed and revealed normal kidney function with a creatinine of 61 µmol/L, urea 30.4, HBA x 6.58, hb 14,4; platelets, 338000 per microliter (mcL) (normal value of 150,000 a 400,000 per microliter (mcL) or (150 a 400 × 109/L); leucocytes, 6900 (normal values under 10.000 cells per mL). Uroculture: *Escherichia coli* multisensible to antibiotics. Some GUSE (general urine sediment exam) with hematuria gives the impression of the infection of urinary tracts (IDX) or recurrent infections of urinary tracts and urinary incontinence. Since the symptoms continue, the patient attends the infectology service unit, which recommends specialized laboratory tests to discard any sexual transmission disease and renal tuberculosis. It was performed urine cytology in serial urine of three for cytologic studies prepared for Papanicolau and Zhiel Nielsen staining (Macroscopic description). Negative for malignancy, abundant inflammatory cells, predominantly macrophages, and lymphocytes (+). Urothelial cells show tiny inflammatory reactive changes, Bacilar flora changes (++), positive *bacillus* acid alcohol resistance (B.A.A.R.) (Zhiel Neelsen staining) for one of the samples.

A molecular test was applied. Real-time PCR confirmed the presence of M. tuberculosis. Next, the patient attends the Unit of Research of the Institute Mexican of Social Security (IMSS) that collects three serial urine. Both acid-alcohol-resistant bacilli (AARB) and GeneXpert were negative. The early *Mycobacterium tuberculosis* diagnoses revealed the presence of the mycobacteria. However, the patient continues with discomfort, microhematuria, and urine infections. Amikacin and phosphodyl recommend due to the patient's allergic to several antibiotics. After five months post-third's positive results except for the urinary incontinence, she attends Nephrology service. Further microbiological, immunological, and molecular tests confirmed the early *MTb* infection. According to the physical examination (PE) of the patient: Height (1.71 m), weight (60 Kg), temperature (36ºC), arterial pressure (130/80 mmHg); heart rate (80 /min), and breathing respiratory (20 resp/min). The patient was observed conscious, oriented, and hydrated, in normal oropharyngeal in CR RsCsRs no aggregations in normal pulmonary area, in the abdomen without compromise, no edemas, of Ms. Is. Physical Examination (PE); height (1.71 m), weight (60 Kg), glucose (ND), temperature (36oC). Arterial pressure (130/80 mmHg); heart rate (80 /min); breathing respiratory (20 resp/min).

Discussion and Conclusion

Urinary tract infections are one of disseminated tuberculosis common in 20% of the individuals infected with *Mycobacterium tuberculosis*. Herein, a brief report of an unsuspected course of Urinary Tuberculosis. The individual from the infectology service. The clinical signs were not very characteristic of no pulmonary TB. An individual refers to urinary incontinence episodes, recurrent urinary infections, and suffering from intermittent stages of microscopic hematuria. Therefore, the initial diagnostic is to discard glomerulopathy and renal tuberculosis. The historical clinic of incontinence urinary requires the evaluation by Urology in the way to make a Chirurgie resolution if it is considered necessary. On nephrology does not require management. At this moment, and in such a case, it requires determining the origin of hematuria. New paraclinical tests on urinary sediment include seric creatinine and urea to evaluate renal function.

Laboratory tests revealed normal kidney function with a creatinine of 61 µmol/L, urea 30.4, hba x 6.58, hb 14,4. Platelets, 338000 per microliter (mcL) (normal value of 150,000 to 400,000 per microliter (MCL). Leucocytes 6900 (normal values under 10.000 cells per mL). Uroculture: *Escherichia coli* multisensible to antibiotics. Some GUSE (general urine sediment exam) with hematuria gives the impression of recurrent infections of urinary tracts and urinary incontinence. Since the discomfort continued, a detailed oncologic and pathological examination was carried out (Figure 1A-B). The results showed urine serial cytologic bacilar flora (++). Acid alcohol-resistant bacillus (BAAR)(+) in one of the series samples. Abundant inflammatory cells, macrophages, and lymphocytes (+), urothelial cells present inflammatory changes reactive, bacilar flora (++). Zhiel Neelsen shows positivity in one of the samples. Molecular assay. RT-PCR in real-time of urine with beta-globin as controls. *M. tuberculosis* (+); *M. bovis* (-). 7500 Fast Real-Time PCR system; Applied BiosystemsTM. The adult individual was evaluated in infectology service by suspected renal tuberculosis, which discards with GenXpert and MGIT culture.

Since the discomfort persisted, a third diagnostic assay in the laboratory research investigation continued as outlined in Figure 1A-B). From the literature, it is well known that biomarkers determination leads to a better understanding of the components that determine the spectrum disease. The reactivation of the dormant mycobacteria, and the progression of the disease [36,43-48], providing thus, a feasible tool to predict or define prognostic or diagnostic tests [50-52]. These assays like tests based on several methodologies: Microbiological techniques, Serological mycobacterial antigen reactivity (Figure 1C; Figure 2) [53], Molecular tools (PCR) [54], and a set of a profile of up and down-regulated genes (i.e. genes that participate in autophagy, innate immue response, MAPKs, cellular transport)(Tables 1A-B). All of them, strengthened the data obtained by early real-time PCR and classical BAAR (Figure 1A-B). Indeed, in previous work, we proposed that these methodologies can be extrapolated to human Tuberculosis [54]. Moreover, Berry *et al*., 2010 [44] reported the blood transcriptional signature in active TB patients.

Collectively, by the data presented here, we can conclude that a combination of clinics and diagnosis leads to a shortcut in UG-TB diagnosis, providing hope and a better therapeutic intervention for patients with unsuspected course of Urinary Tuberculosis.

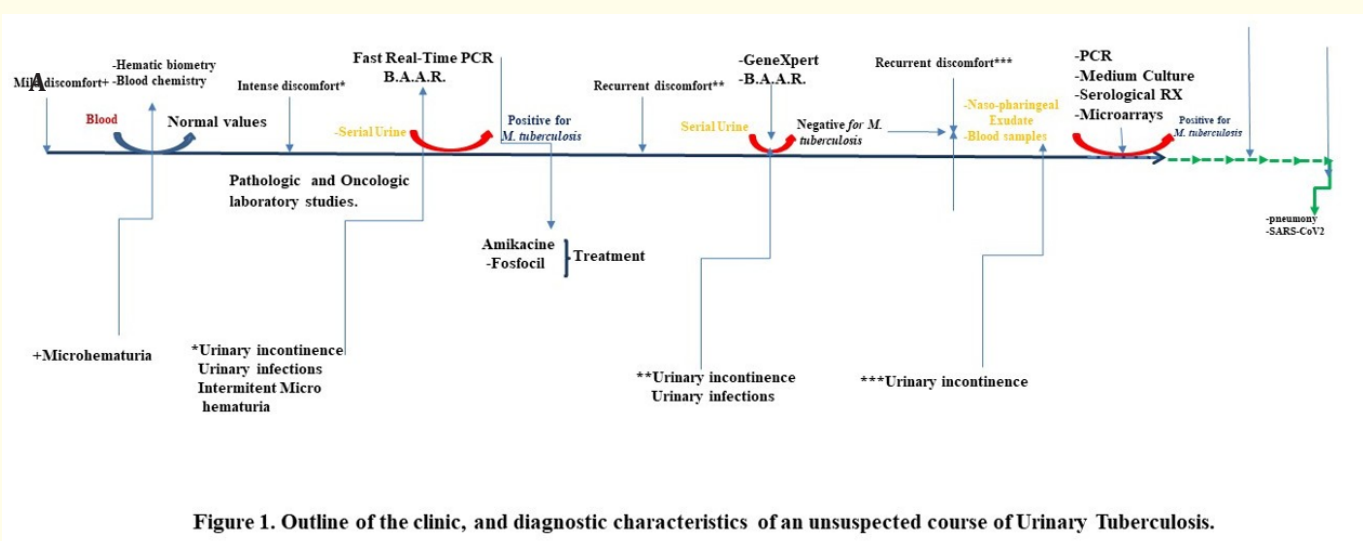

Figure 1. Outline of the clinic, and diagnostic characteristics of an unsuspected course of Urinary Tuberculosis.

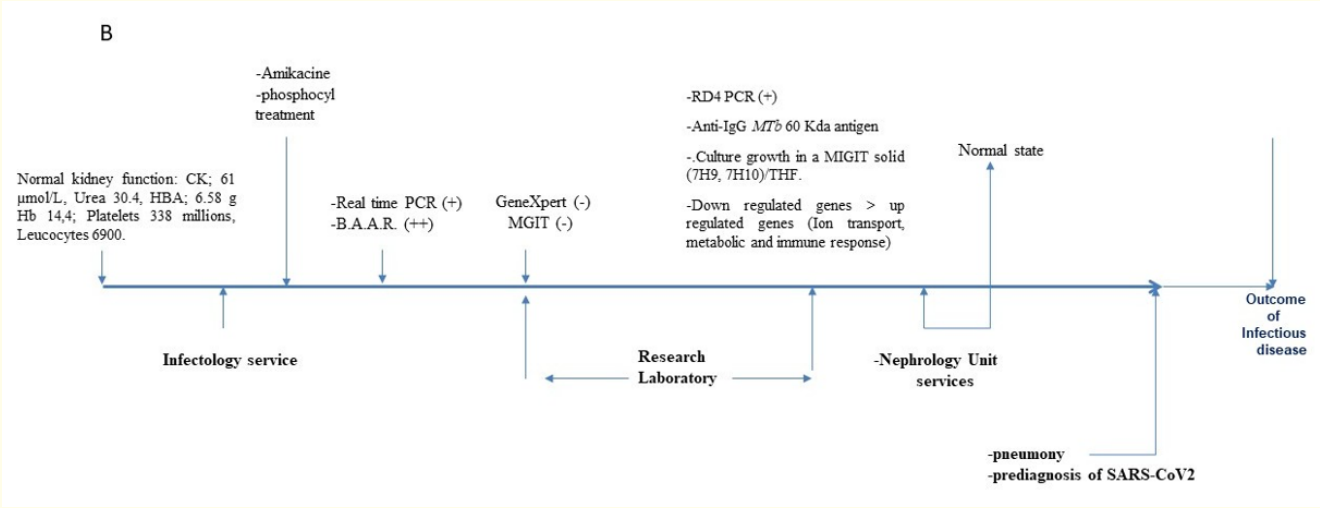

Figure 1. Clinical, and Diagnostic characteristics of an unsuspected course of Urinary Tuberculosis. A. Outline of the clinic and diagnostic characteristics of the patient. B. A summary of the classical (microbiology, biochemical), and no classical (serological reactivity toward mycobacterial antigens serology), molecular methodologies (PCR, real-time PCR, microarrays). C. Scheme of the different methodologies used, of paramount to reach UG-TB diagnostic.

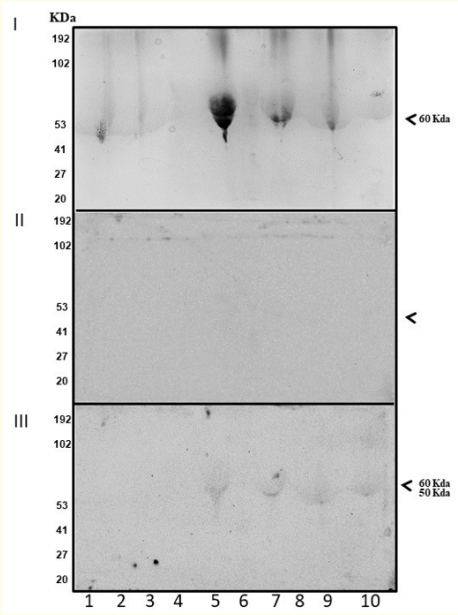

Figure 2. Serological reactivity of IgG antibodies to *Mycobacterium tuberculosis* (MTB) antigens's in an unsuspected course of Urinary Tuberculosis. MTB antigens of the complex of *M. tuberculosis* [(*M. bovis* BCG, *M. bovis,* and the *M. bovis* AN5 (reference strain)] were obtained as reported by Favela-Hernandez., *et al*. 2019. Herein, patients serum reacts predominantly toward a band of proteins of around 50-60 Kda (A). Lane 1: Molecular Weight Markers (MWM). Lane 2. *M. bovis* BCG. Lanes 3-4, *M. tuberculosis* attenuated (HA1). Lane 5, *M. bovis* East. Lane 6, empty. Lane 7, M. bovis AN5). Lane 8, empty. Lanes 9-10, *M. tuberculosis* H37Rv).

A

Code	Gene name	UP (fold change)	Code	Gene name	Down (fold change)
NM_031409	CCR6	4.48	NM_003629	PIK3R3	-2.05
NM_024031	MGC3121	3.545	NM_006293	TYRO3	-2.059
NM_001482	GATM	3.54	NM_001078	VCAM1	-2.128
NM_000579	CCR5	3.1	NM_000358	TGFB1	-2.169
NM_004514	FOXK2	2.874	NM_017874	C20Orf27	-2.179
NM_001570	IRAK2	2.816	NM_003985	TNK2	-2.242
NM_001552	IGFBP4	2.779	NM_003159	CDKI5	-2.274
NM_003327	TNFRSF4	2.761	NM_021252	RAB19	-2.288
NM_022369	FLJ12541	2.71	NM_013272	SLCO3A1	-2.382
NM_006566	CD226	2.563	NM_003844	TNFRSF10A	-2.391
NM_018958	C15orf2	2.513	NM_006068	TLR6	-2.456
NM_020062	SLC24A4RG	2.341	NM_006866	ULRB1	-2.493
NM_019848	SLC10A3	2.295	NM_006648	PRKWNK2	-2.526
NM_001152	SLC25A5	2.274	NM_004172	SLC1A3	-2.563
NM_004566	PFKFB3	2.239	NM_004612	TGFBR1	-2.568
NM_004642	CDK2AP1	2.233	NM_032996	CASP9	-2.746
NM_005228	MOBK1B	2.2	NM_006449	CDC42EP3	-2.867
NM_002465	EGFR	2.187	NM_025159	CXorf21	-3.002
NM_003242	MYBPC1	2.158	NM_004512	IL11RA	-3.363
NM_007217	TGFBR2	2.149	NM_006564	CXCR6	-3.402
NM_004251	PDCD10	2.107	AF284434	IL1RL2	-3.539
NM_019895	RAB8A	2.093	NM_002170	IFNA8	-4.427
NM_017903	C3orf4	2.066	NM_019111	HLA-DRA	-4.482
NM_002032	FLJ20618	2.058	NM_004625	WNT7A	-4.556
NM_017515	SLC35E2	2.033	L34093	HLA-DQA1	-5.04

B

Pathway (Up)	symbol gene	fold change	p value
Loss of function of TGFBR2 in cancer	TGFBR2	2.15	0.002
Loss of function of TGFBR1 in cancer	TGFBR2	2.15	0.004
TGF-β receptor signaling in EMT	TGFBR2	2.15	0.017
Signaling by TGF-beta receptor	TGFBR2	2.15	0.024
SMAD2/3-phosphorylation motif mutants in cancer	TGFBR2	2.15	0.004
Loss of function of SMAD3 in cancer	TGFBR3	2.15	0.024
IRAK4 deficiency(TLR2/4)	IRAK2	2.6	0.014
Trafficking of GLUR2 containing AMPA receptors	CDK2AP1	2.23	0.019
HSF1 activation	HSF2	2.3	0.05
Pathway (down)	**symbol gene**	**fold change**	**p value**
Loss of function of TGFBR2 in cancer	TGFB1	-2.17	2,28 X 10-5
Loss of function of TGFBR1 in cancer	TGFBR1	-2.57	6.96 X 10-5
TGF-β receptor signaling in EMT	TGFBR1	-2.57	0.001
Signaling by TGF-β receptor	TGFB1	-2.17	0.002
Downregulation of TGF-β receptor signaling	TGFB1	-2.13	0.008
Dimerization of procaspase 8	TNFRSF 10A	-2.39	0.002
Regulation of cFLIP	TNFRSF 10A	-2.39	0.051
IRAK4 deficiency (TLR 2/4)	IRAK2	-2.46	0.077
IL-36 pathway	IL1RL2	-2.13	0.043

-The pattern of up and down regulated genes were determined using DNA microarray. cDNA was prepared from RNA using the KIT (first-strand cDNA labeling KIT (Invitrogen). *M. tuberculosis* DNA Microarrays prepared and hybridized with cDNA's patient or healthy individual (A)(Unit of Microarray, IFC-UNAM, Mexico City). The microarray analysis using genarise. Up and Down-regulated genes filter for two cutoffs, one for Z-Score higher than 1.5 and the second, with Z –Scores higher than 2 (> 1.5 and 2.0 SD) ($P < 0.05$) while Graphpad 7.0 program software for heat maps analysis (A). Reactome functional analysis (B) based on the probability (p value) that a reaction occur in a pathway (Fabregat et al., 2017).

Figure a. Most up and down regulated genes in blood with unsuspected course of urinary tuberculosis.

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Ethics Approval and Consent to Participate

The study and all the procedures for medical research involving human subjects, including research on identifiable human material and data were performed under the principles of the Declaration of Helsinski, and approved by the ethic commitee in Research of the Zacatecas, General Hospital "Luz Gonzalez Cosio" CONBIOETICA-32-CEI-001-20180807.

Consent for Publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review.

Competing Interests

The authors declare no competing of interests.

Availability of Data and Material

Data will be shared following institutional guidelines. The review of the literature was based on search and data from Pubmed database without limitation to 2021.

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Author's Contributions

G.G.G.M. conceptualization, methodology, analysis and writing. L.A.A.G. collaboration in patient's contact, discussion. A.A.C.; I.T. and J.M.F.H. Reviewing of the report. All authors have read and approved the manuscript.

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