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Case Report

Detection of the Lassa Virus in a Group of Odontogenic Bone Tumor Tissues

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Abstract: Odontogenic bone tumor (OT) is a rare pathology in the world, but it is very common in developing countries; its etiology is still unknown, and it causes serious deformities of the mandible and maxilla if it is not operated upon soon. Lassa virus (LASV) belongs to the *Arenaviridae* family, and its reservoir is a rodent of the genus *Mastomys*. The transmission of the LASV to humans can occur through ingestion or inhalation by contact with dirty objects, the consumption of contaminated food, or exposure to wounds, as rodents shed the virus in their urine and excrement. In this observational study, we aim to evaluate the presence of LASV in OT patient tissues collected in the Democratic Republic of the Congo. For this purpose, a group of nine patients affected by OT were enrolled, and the tissues derived from the surgery were collected. In total, 81.5% of the tissues were positive for LASV presence. Interestingly, we found that not only was the tumor LASV-positive, but in some cases, the bone was close to the tumor and the oral mucosa lining. These preliminary data could suggest the hypothesis that LASV may be involved with the onset of OT.

Keywords: Lassa virus; LASV; arenavirus; odontogenic fibrous-bone tumor; ameloblastoma

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1. Introduction

Odontogenic fibrous-bone tumors (OTs) are uncommon neoplastic lesions of the maxilla and mandible, which present difficulties in diagnosis and therapy. Although classified as a benign tumor, overall odontogenic tumors are characterized by local aggressiveness and pathology relapse tendencies, thus systematically requiring demolition interventions that negatively affect the patient's aesthetics and quality of life [1,2]. The incidence of OT is high in Sub-Saharan African countries where children and young adults are the most affected population [3]. Ameloblastoma, the most common odontogenic tumor of epithelial origin, is classified as a benign tumor. However, the management of ameloblastomas is quite controversial as 5-year recurrence still shows high rates among patients [3,4].

Odontogenic fibroma, ossifying fibroids, fibrous dysplasia, and odontogenic fibro myxoma are the other most common types of OT [2,3].

In most Sub-Saharan African countries, the diagnosis of OT is underestimated due to inadequate registered epidemiological and clinical data, including histological analyses of the tissue samples. Furthermore, the affected people are often marginalized because of the severe functional impairment of the aero-digestive tract and the phenotypic appearance caused by the tumor. Limited resources, high costs of treatment, and fear of surgery are the major factors contributing to late diagnosis and treatment [1,3].

To date, the etiology of OTs in humans is still unknown. Recently, some authors have reported molecular results about altered gene signatures in ameloblastoma, and others have attempted to evaluate the presence of the human papillomavirus (HPV) and Epstein–Barr virus (EBV) in OT tissues as a hypothetical etiological agent. However, there is still insufficient data in the literature to consider these viruses as markers of prognosis as it happens in cervical or nasopharyngeal cancer [5–9]. Previously, observing some epidemiological data in the Lacor Hospital in Uganda, we discussed the hypothesis that the Lassa virus (LASV) could be a virus related to OT [10].

LASV (*Lassa mammarenavirus* species) belongs to the arenavirus genus and Arenaviridae family. It is responsible for Lassa hemorrhagic fever (LF) in the Sub-Saharan African region. Rats and bats are the natural hosts of LASV, and the spillover occurs through urine and excrement. However, these animals are the only available delicacy and cheap source of protein in the region and are therefore commonly consumed as food. Often, humans are infected with LASV through exposure to meat, food, or household items contaminated with urine or feces. It is mainly children who find this food source and consume it in large quantities [10,11].

The association between OTs and LASV has not been established in humans yet [12]. This is an observational study where, by using a specific diagnostic kit, we detected the presence of LASV in OT tissues extracted from a restricted cohort of patients recruited in the Democratic Republic of Congo. This initial evidence suggests a possible rationale for future investigations of LASV in these tumors, where a larger casuistry of patients is peremptory.

2. Materials and Methods

2.1. Study Design and Participants

In this observational study, OT patients were consecutively enrolled at Glory Clinic in Kinshasa for surgical resection, and they or their legal guardians provided written informed consent. The duration of enrollment was eight months. Demographic, clinical, and laboratory data were obtained in accordance with ethical approval. Research on human samples was conducted in accordance with all relevant guidelines and regulations, including the Declaration of Helsinki. Ethical approval was obtained from the Ministry of Public Health of the Democratic Republic of the Congo (n. 394/CNES/BN/PMMF/2020 of 04/20/2020).

The inclusion criteria that we have established were as follows: be a patient with odontogenic and maxillofacial bone tumours, aged 0–80 years old; be a resident in Kinshasa and surrounding areas. The exclusion criteria are as follows: residents of the non-selected study area; patients with contraindications for surgery as determined by the attending surgeon; refusal to provide signed informed consent or assent.

The diagnostic hypothesis based on clinical and radiographic parameters was subsequently supported by a histological examination of the anatomic pathologist [13]. For the patients who showed a difficult pre-operative situation during the clinical examination, a 3D CT scan (axial computed tomography) was used, which is an innovative technique for obtaining three-dimensional images of the teeth, jaw bones, and soft tissues. For the diagnosis, also obtained with the evaluation of the histological analysis of the tissue, the classification criteria described in the update released in the 5th edition of the World Health Organization (WHO) Classification of Head and Neck Tumors (2022) were applied, which includes cysts of the jaws, odontogenic tumors, giant cell lesions and bone cysts, and bone

and cartilage tumors [13]. The diagnosis and clinicopathological characteristics of patients are reported in Table 1.

Table 1. Clinicopathological characteristics of patients.

Characteristics	*n* (%)
Total patients	9
Female	3 (33.3%)
Male	6 (66.6%)
Sex ratio (M:F)	
Age (y), mean ± SD	21.6 ± 10.7
Median (IQR), years	15 (13–33)
Range, years	9, 36
Age group (y), *n* (%)	
<18	5 (55.5%)
18–24	0
25–30	1 (11.1%)
>30	3 (33.3%)
Diagnosed with, *n* (%)	
Ossifying fibroma (OF)	7 (77.7%)
Ameloblastoma (AM)	1 (11.1%)
Pseudocarcinomatous hyperplasia (PH)	1 (11.1%)
Patient with relapse, *n* (%)	4 (44.4%)
Location *n* (%)	
Mandible	9 (100%)
Age Type, *n* (%)	
<18 AM (%)	1 (11.1%)
>18 AM (%)	0
<18 OF (%)	3 (33.3%)
>18 OF (%)	4 (44.4%)
<18 PH (%)	1 (11.1%)
>18 PH (%)	0

2.2. Histological Staining

Histology and diagnosis of the tissue sections were carried out at the Pathological Anatomy Laboratory of Glory Clinic in Kinshasa. Briefly, de-paraffinized, hydrated serial sections of the tissues were stained with hematoxylin and eosin (H&E) using standardized protocols for clinical diagnostics. The sections were examined under a light microscope Leica (Model No. DM1000 LED, Leica Microsystems, Wetzlar, Germania).

2.3. Viral RNA Extraction and RT-qPCR

We collected 32 tissues in total (tumor, oral mucosa lining the tumor, and bone close to the tumor) from 9 OT patients. The tissues derived from surgery were immediately immersed in RNAlater (Thermo Fisher Scientific, Waltham, MA, USA) to inhibit RNA degradation. Viral RNA was extracted using the QIAamp Viral RNA Mini Kit according to the manufacturer's instructions (Qiagen, Hilden Germany). The quantitative PCR method was previously described by Kafetzopoulou and colleagues [13].

Briefly, to evaluate the presence of Lassa viral genomes, the Altona 2.0 qPCR assay was used following the indications of the supplier (RealStar Lassa Virus RT-PCR Kit 2.0 CE, n° 642013 version 03/2019, Altona Diagnostics, Hamburg, Germany).

This is a diagnostic kit that uses multiple genomic sequences of LASV nucleic acid as target regions of the probes, such as L segment (7.3 kb long) coding for the RNA-dependent RNA polymerase and S segment (3.4 kb long) coding for the glycoprotein GPC, to drastically reduce the likelihood of false-negative results (Figure 1). The kit consists of two probe mix assays, one targeting the LASV GPC gene and another targeting the LASV L gene. These assays include a heterologous amplification system (Internal Control, IC) to identify possible PCR inhibition and to confirm the integrity of the reagents. The IC target must be added to the RNA of the sample at the time of viral RNA extraction. Each RNA sample was normalized to 3 ng/µL, and 10 µL of the extracted RNA was added to 20 µL of the reaction mix. As technically negative samples, reaction mixtures with water were loaded onto the plates for each real-time PCR reaction.

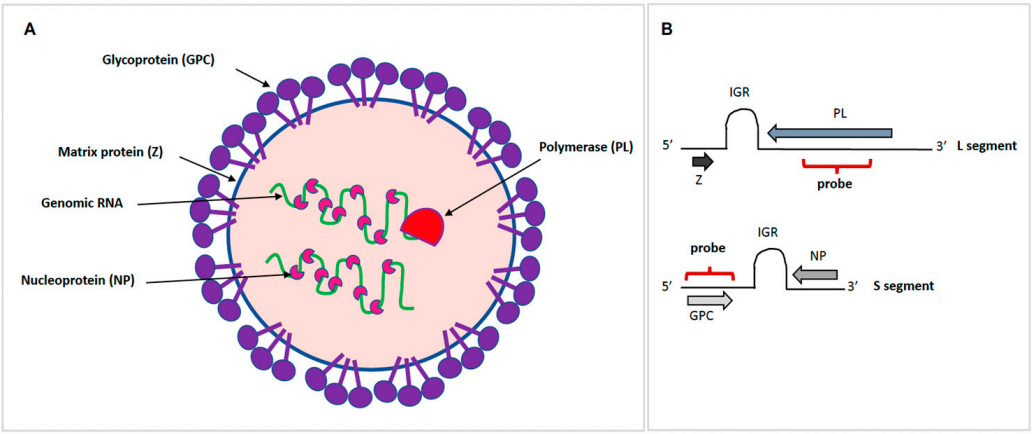

Figure 1. LASV structure and genome organization. (**A**) LASV is an enveloped virus with a biseg-mented strand RNA. LASV is surrounded by a lipid double membrane containing a glycoprotein (GPC) complex involved in receptor binding on cells and cell entry. Beneath this envelope is a protein layer (Z) that plays an important role in viral assembly and budding. LASV is surrounded by a lipid double membrane containing a glycoprotein (GPC) complex involved in receptor binding on cells and cell entry. Under this envelope is a protein layer (Z) that plays an important role in viral assembly and budding. The viral genome (green segments) is complexed by viral ribonucleoproteins (NPs). The viral RNA-dependent RNA polymerase (PL) protein is associated with viral ribonucleoproteins and comprises the minimal components required for LASV genome replication and gene transcription. (**B**) Each of the two viral RNA segments has an ambisense transcript to direct the synthesis of two viral proteins in opposite orientations. The large (L) RNA segment (7.2 kb) encodes the viral PL and Z, and the small segment (S) RNA (3.5 kb) encodes viral GPCs and NPs. The position on the genome of the two probe mixes used in qPCR is shown with a red segment (probe).

The real-time instrument used was ABI Prism® 7500 Fast SDS (Applied Biosystems, Waltham, MA, USA).

RT-qPCR assays have been performed in triplicate, and samples reaching threshold cycle (Ct) values under 35 have been set as positive.

The procedures described in this paragraph were conducted at the Department of Virology of the University Clinic of Kinshasa.

2.4. Statistical Analysis

Statistical analysis was carried out using a two-tailed *t*-test by using GraphPad Prism (version 10.2.0).

3. Results

3.1. Presentation of the Cases

The clinical characteristics of the patients are previously reported in Table 1. The age range of the patients was between 9 and 36 years with a median of 15, and 55.5% of the patients were under 18; therefore, the patients were all extremely young. In total, 44.4% of patients exhibited the development of at least one recurrence a few months after the demolition surgery.

At the time of the visit, the patients underwent radiography and/or CT scans to confirm the tumor. However, the patients presented evident facial deformities. The common clinical signs and symptoms were fever; headache; soar throat; general body weakness; joint pain; and difficulty in chewing, breathing, and speaking due to the anatomical deformation of the mouth. In an advanced stage, notable episodic and uncontrollable weight loss (from cachexia to refractory cachexia with a body mass index well below 18.5 kg/m^2) was observed. The serum alteration of hemoglobin (low), albumin (low), and total protein (low) were revealed. Some examples of patients having a lesion that promoted the expansion of the OT at the time of diagnosis and the respective CT scans are shown in Figure 2.

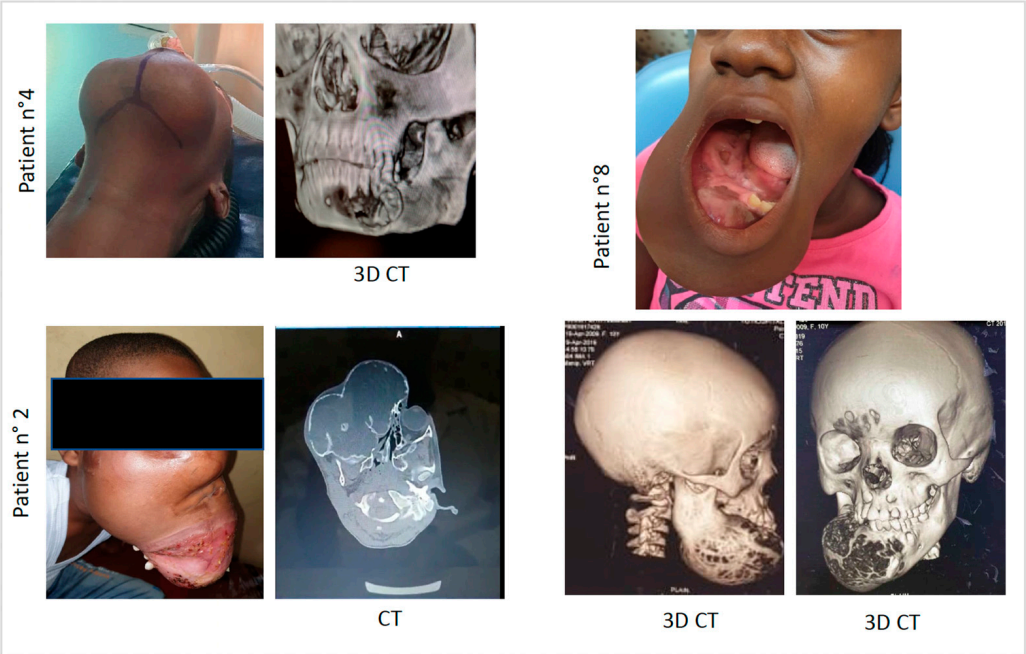

Figure 2. Photographs upon admission to the hospital and conventional CT and 3D CT scans show the large expansile lesions that break down the physiological bone structures of the mandible and maxilla. Patient 2: Preoperative CT image acquired in axial view; patients 4 and 8: 3D reconstruction CT images; 3D, 3 dimensional.

The patients presented tumors mostly categorizable as an ossifying fibroma. However, the histological evaluation in detail for each patient is reported in Table 1.

Some examples of the images of neoplastic tissues obtained with hematoxylin-eosin staining are shown in Figure 3.

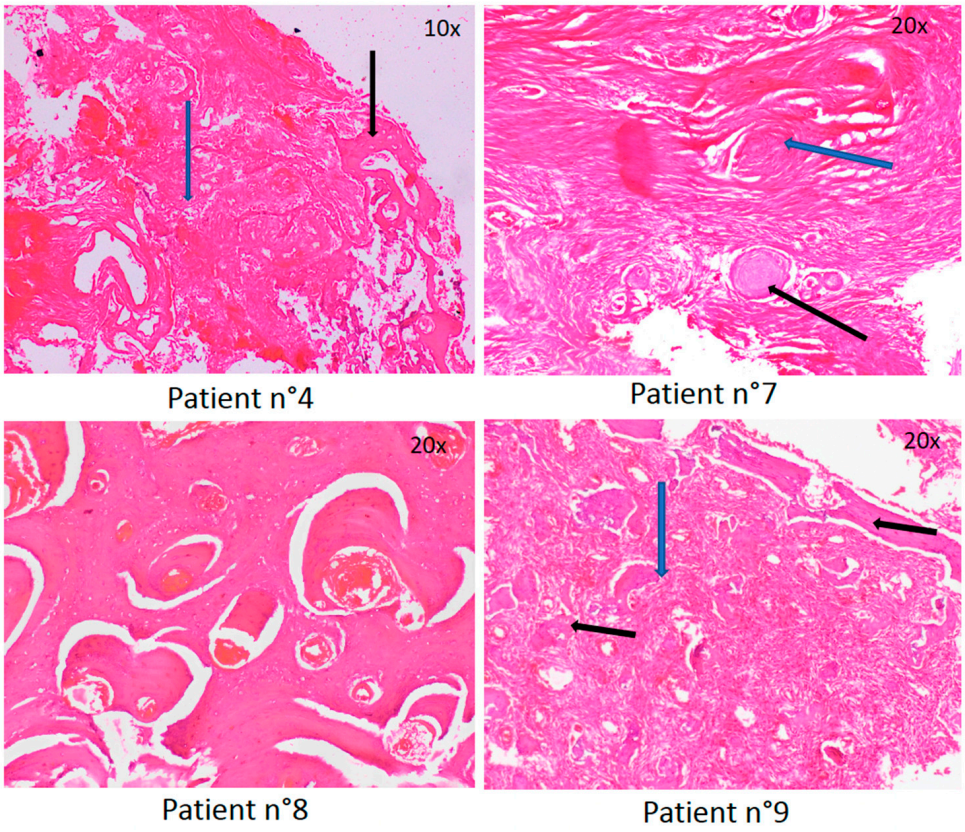

Figure 3. Histology of some tissues from OT patients. Patient n° 4: H&E staining. Note a proliferation of spindle cells (blue arrow) that confirm the foci of bone metaplasia (black arrow). Patient n° 7: H&E staining. Note a proliferation of spindle cells (blue arrow) that confirm the foci of bone metaplasia (black arrow). Patient n° 8: H&E staining. Mature stage of the osteoid osteoma lesion showed irregular bony trabeculae lines. Patient n° 9: H&E staining. There is a proliferation of spindle cells (blue arrow) containing foci of bone metaplasia (black arrow).

3.2. Molecular Finding

OT excision surgery was performed in the Glory Clinic/FESMA of Kinshasa, and RT-qPCR analyses were performed by the Department of Virology at the University Clinic of Kinshasa.

To test the presence of the Lassa virus (LASV) in odontogenic fibro-bone tumor (OT) tissues, quantitative PCR reactions were performed on RNA extracted from all collected tissue samples. We used a heterologous internal control (IC) provided by the kit as a control of the sample preparation procedure, which was added during the nucleic acid extraction procedure. In the amplification reactions, a negative control (NC) and a positive control (PC) supplied by the kit were used. All patients were positive for the presence of LASV.

At the time of surgical excision, two to four tissue samples were taken from each patient, including the OT, a bone fragment at the tumor margin showing tumor morphology, and a piece of oral mucosa covering the tumor. We considered five samples as "Invalid" as they did not show PCR amplification either in or above the tissue in the internal control (IC). Therefore, out of the 32 samples collected, we evaluated 27 samples. From this molecular analysis, we reported that 22 tissues were found to be positive (81.5%) for the presence of LASV, and 5 were negative (Figure 4).

Furthermore, we analyzed the results of RT-qPCR considering the specific tissues. We found that not only was the tumor sample Lassa-positive, but the bone was also close to the tumor and the oral mucosa lining (Figure 5). Although two tumor samples were negative for the presence of the Lassa virus, they were derived from patients (1 and 8) who presented positive bone and mucosal tissues (Figure 5).

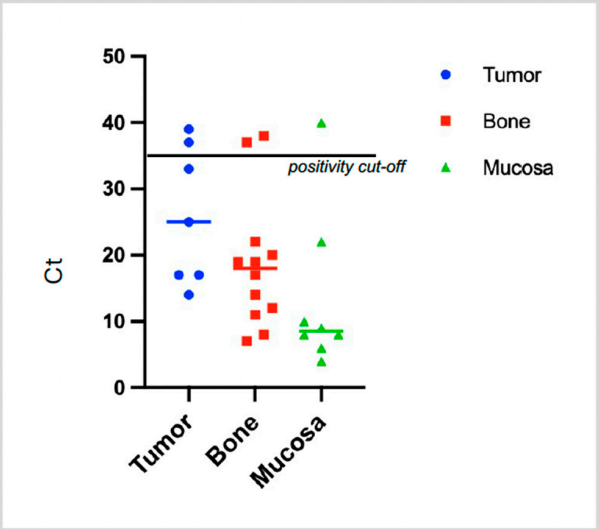

Figure 4. RT-qPCR analysis on OT tissues (N = 27). In the graph, the red line represents the ct cut-off (35-cycle threshold). The bars represent the mean of the ct obtained from each tissue analyzed in triplicate. Black bar: LASV-positive tissues (81.5%); red bar: LASV-negative tissues (18.5%).

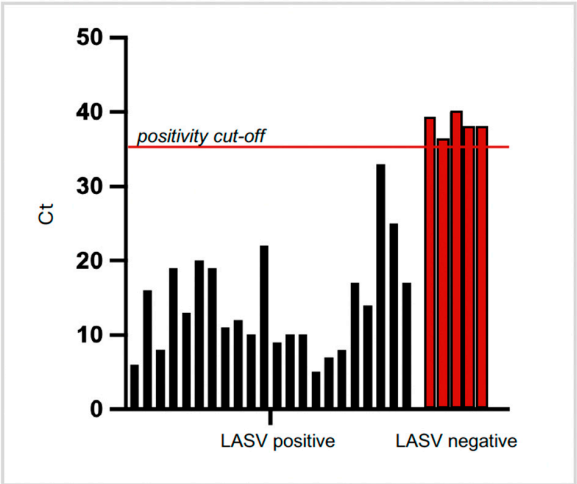

Figure 5. RT-qPCR analysis showing LASV positivity in the specific tissue collected from the OT patients, as described in the Material and Methods. In the graph, the black line represents the ct cut-off (35-cycle threshold). The scatter plot shows the ct obtained from each tissue analyzed in triplicate. The samples above the CT cut-off bar are considered negative for the presence of LASV.

4. Discussion

The findings described in this observational case study, although based on a small group of patients, provide intriguing preliminary data about the presence of the Lassa virus (LASV) in the odontogenic tumor tissues (OTs).

Our working hypothesis was based on the fact that the high incidence of OT tumors in Sub-Saharan countries could be related to dietary habits and therefore to the presence of LASV in the most consumed food [1,6,10,11,14]. Human infection could be explained by the fact that the population eats rat meat as a source of protein and drinks water contaminated by LASV-infected rat urine and feces [10,11]. The incidence of OT in the young and pediatric population in Africa is higher than in other countries [15–17], and this represents the group of young people and children who mainly eat meat, hunt rats, and make skewers to sell in the markets [10]. OTs are rare lesions derived from the epithelial and/or mesenchymal elements of the tooth-forming apparatus and are found primarily within the jawbones [2,18].

Several viruses, named oncovirus, have been identified as etiopathogenic agents for several tumors as they can induce long-term inflammation by suppressing the immune system and promote gene mutation [19,20]. Recently, the only reported case of the presence of arenavirus in an odontogenic tumor was observed in a captive bred red tail boa (*Boa constrictor constrictor*) [21]. In this reptile, an intraoral mass from the buccal gingiva was diagnosed as odontogenic fibromyxoma, a tumor very similar to those observed in humans. Interestingly, the virus was also found in the tissue of the cancer recurrence within the same snake.

LASV is responsible for Lassa fever, which is endemic to various regions of West Africa, but this range seems to be increasing [22]. Lassa fever control and prevention efforts remain hampered by a limited basic understanding of the true incidence of the disease, as these African regions often lack epidemiological records, and they are also hampered by the poverty of the majority population who cannot access clean food and water [10,11,14,20,22]. Recently, LASV has been identified as one of the most threatening spillover viruses among known pathogens, and it is considered among risk factors due to the high population of the natural host species and its ability to mutate by evading cell-mediated immunity [23]. The pathogenesis of Lassa fever is not fully understood, as are the various molecular mechanisms of immune evasion and any long-term effects of the infection [23,24]. Neurological problems are common in patients who have contracted LASV, and these manifest as memory loss, ataxia, muscle pain, and sensorineural hearing loss (SNHL). SNHL is caused by the irreversible damage of cochlear hair cells, and several studies using animal models have shown that LASV-induced SNHL is entirely or at least partially caused by an immune-mediated process [25]. Interestingly, cochlear hair cells appear to be directly infected by LASV, resulting in irreversible damage [25]. It has been shown that macrophages and dendritic cells, which belong to innate immunity, are the cells targeted by LASV in the first phase of the infection [26]; therefore, they are not activated, as evidenced by the lack of expression of their specific cytokines and are unable to present antigens to T lymphocytes, explaining the condition of T cell tolerance to the LASV.

From this scenario, we can hypothesize a similar mechanism of the inflammatory state in which the connective tissue adapts. The initial transformed cells become cancerous, implementing different strategies to counteract immune responses, including the impairment of antigen presentation, the activation of negative costimulatory signals, and the development of immunosuppressive factors.

This result could pave the way for further research aimed at the role of LASV in the characterization of the inflammatory state that is hypothetically driven by LASV in the pathogenesis of some odontogenic tumors (Figure 6).

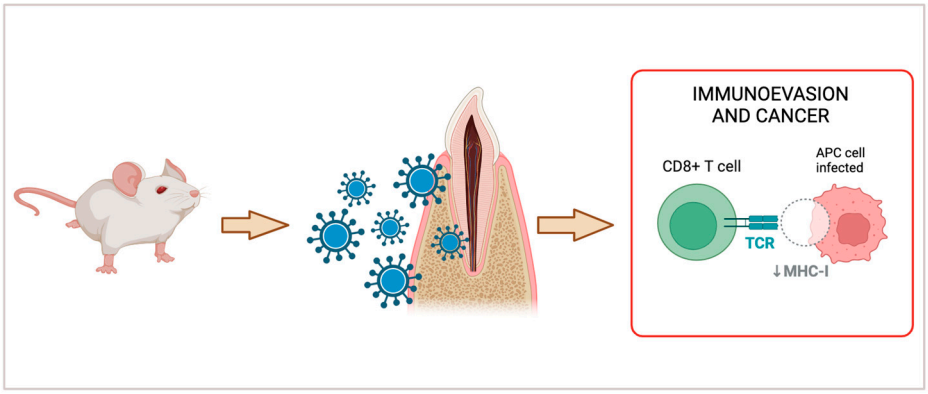

Figure 6. Mechanism hypothesis. Rodents are the major reservoir of the Lassa virus (LASV). Rats are the main source of food [11], and we hypothesize that the virus can also locally infect the tissues of the oral cavity in a similar mechanism as HPV in the oral mucosa and cervix [8]. LASV enters cells via receptor-mediated endocytosis to transcribe its viral protein [25,26]. LASV evades immunity through many mechanisms, including infecting antigen-presenting cells (APCs) or T lymphocytes directly [25,26]. Figure created with BioRender.com.

OTs are characterized by local aggressiveness and postoperative recurrence, even several times until the total demolition of the mandible and/or maxilla, finally causing the patient's death [1,2,17]. Our finding suggests that the detection of the Lassa virus in surrounding tissues after OT resection surgery may represent a prognostic factor for tumor recurrence.

To date, the most common treatment used to manage odontogenic tumors is the surgical resection of the lesion [2]. For the treatment of the Lassa virus, antiviral favipiravir and a human monoclonal antibody cocktail have shown efficacy in rodent animal models, and they might show promise in future human clinical trials [27,28]. The antiviral Ribavirin is only effective if treatment starts in the very early stages of Lassa virus infection [28]. Many efforts are invested in developing a vaccine against the Lassa virus, which has been non-existent to date, and this could be the only option for the prevention and treatment of Lassa fever and, at this point, the onset of odontogenic tumours [27–30].

From the point of view of basic research, it is necessary to investigate the molecular mechanisms of the infection of LASV in the connective tissues of the oral cavity by in vitro experiments and in vivo models, and further corroboration and expansion of the present findings with larger sample sizes across multiple centers are warranted.

Very recently, the identification of LASV genotypes capable of spillover from rodents to humans in Sierra Leone was reported through a comparison of human-derived viral samples, with samples collected from animal reservoirs [31,32]. We are therefore convinced that the genotyping of the kind of LASV identified in OT tissues could also be of significant interest to shed light on the involvement of LASV in tumor onset and recurrence.

5. Conclusions

To our knowledge, for the first time, this study documented the presence of the Lassa virus (LASV) in the odontogenic fibro-bone tumor (OT) tissues collected from nine participants recruited at Kinshasa in the Democratic Republic of Congo. We reported LASV positivity in 81.5% of the analyzed tissues. Overall, this bulk of evidence is at a preliminary stage, and the hypothesis should be investigated in a larger number of patients by inserting a control group.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and ethical approval was issued by the Ministry of Public Health of the Democratic Republic of the Congo (n. 394/CNES/BN/PMMF/2020 of 04/20/2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data are available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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