Telemicroscopy: A Sustainable Model for Integrating Electron Microscopy into Medical Diagnosis in Brazil

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Abstract

Introduction: Telemicroscopy is a technique that enables remote access to microscopy platforms, allowing the analysis of samples at a distance. It has great potential in aiding medical diagnosis, including ultrastructural pathology with electron microscopy. **Objective:** To establish a sustainable model for integrating electron microscopy tools into the medical diagnostic portfolio through the implementation of telemicroscopy hubs applied to ultrastructural pathology. **Methodology:** Methodologies based on protocols from international reference centers were adopted to structure a workflow adapted to national centers. Three interaction strategies were tested: asynchronous telemicroscopy, on-site visits, and synchronous telemicroscopy. **Results:** The implementation followed adapted protocols, testing the interaction strategies. Synchronous telemicroscopy shows potential for democratizing access to electron microscopy. An initial digital image bank was created. The results demonstrate the operational feasibility of the proposed model. **Conclusions:** Proper sample preparation and continuous interdisciplinary communication are essential for telemicroscopy. This model has the potential to democratize access to electron microscopy, reduce regional inequalities, and consolidate a collaborative network within the country. The generated databases support education, research, and future use of artificial intelligence in the differential diagnosis of pathologies.

Key-words: telemicroscopy, differential diagnosis, transmission electron microscopy, ultrastructural pathology

Resumen

Telemicroscopía: Un Modelo Sostenible de Integración de la Microscopía Electrónica al Diagnóstico Médico en Brasil

Introducción: La telemicroscopía es una técnica que permite acceso remoto a plataformas de microscopía, facilitando análisis de muestras a distancia. Tiene un gran potencial en el apoyo al diagnóstico médico, incluyendo la patología ultraestructural con microscopía electrónica. **Objetivo:** Establecer un modelo sostenible de integración de microscopía electrónica al portafolio de diagnóstico médico, mediante la implementación de núcleos de telemicroscopía aplicada a la patología ultraestructural. **Metodología:** Se adoptaron metodologías basadas en protocolos de centros internacionales de referencia para estructurar un flujo de trabajo adaptado a los centros nacionales. Se probaron tres estrategias de interacción: telemicroscopía asincrónica, visitas presenciales y telemicroscopía sincrónica. **Resultados:** La implementación siguió protocolos adaptados, probando las estrategias. La telemicroscopía sincrónica muestra potencial para democratizar el acceso a la microscopía electrónica. Se creó un banco de imágenes digitales. Los resultados evidencian la viabilidad operacional del modelo propuesto. **Conclusiones:** La preparación adecuada de la muestra y la comunicación interdisciplinaria continua son fundamentales para la telemicroscopía. Este modelo tiene potencial de democratizar el acceso a la microscopía electrónica, reducir desigualdades regionales y consolidar una red colaborativa en el país. Las bases de datos generadas apoyan la educación, investigación y el futuro uso de inteligencia artificial en el diagnóstico diferencial de patologías.

Palabras clave: telemicroscopía, patología ultraestructural, microscopía electrónica de transmisión, diagnóstico diferencial

Resumo

Telemicroscopia: Um Modelo Sustentável de Integração da Microscopia Eletrônica ao Diagnóstico Médico no Brasil

Introdução: A telemicroscopia é uma técnica que permite o acesso remoto a plataformas de microscopia, possibilitando a análise de amostras à distância. Tem grande potencial no auxílio ao diagnóstico médico, incluindo patologia ultraestrutural com microscopia eletrônica. **Objetivo:** Estabelecer um modelo sustentável de integração de ferramentas de microscopia eletrônica ao portfólio de diagnóstico médico, através da implantação de núcleos de telemicroscopia aplicada à patologia ultraestrutural. **Metodologia:** Foram adotadas metodologias baseadas em protocolos de centros internacionais de referência para estruturar um fluxo de trabalho adaptado aos centros nacionais. Testaram-se três estratégias de interação: telemicroscopia síncrona e assíncrona e visitas presenciais. **Resultados**: A implementação seguiu protocolos adaptados, testando as estratégias de interação. A telemicroscopia síncrona mostra potencial para a democratização do acesso à microscopia eletrônica. Um banco de imagens digitais inicial foi criado. Os resultados evidenciam a viabilidade operacional do modelo proposto. **Conclusões:** O preparo adequado da amostra e a comunicação interdisciplinar contínua são fundamentais para telemicroscopia. Este modelo tem o potencial de democratizar o acesso à microscopia eletrônica, reduzir desigualdades regionais e consolidar uma rede colaborativa no país. Os bancos de dados gerados auxiliam na educação, pesquisa e futuro uso de inteligência artificial no diagnóstico diferencial de patologias.

Palabras-chave: telemicroscopia, diagnóstico diferencial, microscopia eletrônica de transmissão, patologia ultraestrutural

INTRODUCTION

Telehealth has experienced exponential growth in recent years, offering innovative forms of healthcare and medical care. Constantly evolving technologies offer opportunities for access to healthcare services for those who are homebound or live in underserved areas, as well as enabling patients with rare diseases to receive care from specialists located in other regions [1,2]. However, telehealth not only expands patients' access to healthcare professionals but also offers physicians the opportunity to use tools that optimize the differential diagnosis of various pathologies. This is the case with telemicroscopy, a technique that allows remote access to different microscopy investigation platforms[3]. In telemicroscopy, the user can analyze their sample remotely using virtual data sharing tools. In this way, hospitals and diagnostic laboratories can send samples to the imaging center, and the pathologist can analyze the images obtained remotely [3].

Telemicroscopy has great potential in assisting medical diagnosis, including classic histopathology (with the aid of light microscopy) and ultrastructural analysis (with the aid of electron microscopy). Ultrastructural analysis is becoming an increasingly important complementary and, sometimes, differential tool in medical diagnosis [4]. This is because the diagnosis of some pathologies depends on high-resolution images, with resolutions only achievable at the electron microscopy level. This is the case of primary ciliary dyskinesia, a rare condition with autosomal recessive inheritance, frequently manifested by chronic respiratory infections from the first years of life [5]. In addition to the scarcity of epidemiological data and phenotypic heterogeneity, the lack of accurate and sensitive diagnostic methods contributes to delays and, frequently, to misdiagnosis of primary ciliary dyskinesia[6].

European and North American diagnostic guidelines recommend transmission electron microscopy (TEM) as part of a set of tests for diagnostic confirmation. TEM is used to identify ultrastructural defects in cilia[7], such as the absence or anomalies of the outer and inner dynein arms, defects in the microtubules that make up the axoneme, and complete disorganization of the typical cylindrical structure[8–10]. In addition to primary ciliary dyskinesia, ultrastructural analysis by TEM can assist in the diagnosis of other diseases, such as minimal change nephrotic syndrome [11], focal segmental glomerulosclerosis[12], alveolar capillary dysplasia[13], and epidermolysis bullosa [14].

Currently, there are more than 700 electron microscopes in operation in Brazil, according to the Brazilian Society of Microscopy and Microanalysis, although they are asymmetrically distributed across the country, with almost 81% located in the Southeast region[15]. Despite some centers offering diagnostic services using electron microscopy, most microscopes have been used only for academic and research purposes, not for diagnostic purposes. This reality highlights the limited access of pathologists to the installed base of electron microscopy in the country and reinforces the need for the establishment of tools for remote use of these instruments. The implementation of telemicroscopy could expand pathologists' access to electron microscopes, assisting and accelerating the differential diagnosis of many pathologies, offering an immediate benefit to Brazilian society.

Given the extensive installed base of electron microscopy in the country and the growing demand for diagnosis through ultrastructural pathology, the objective of this work is to establish a sustainable model for integrating electron microscopy tools into the medical diagnostic portfolio in the country through the implementation of a tele-microscopy center applied to ultrastructural pathology. Therefore, this is a qualitative study, describing the initial stage of structuring the workflow inherent in the implementation of the center.

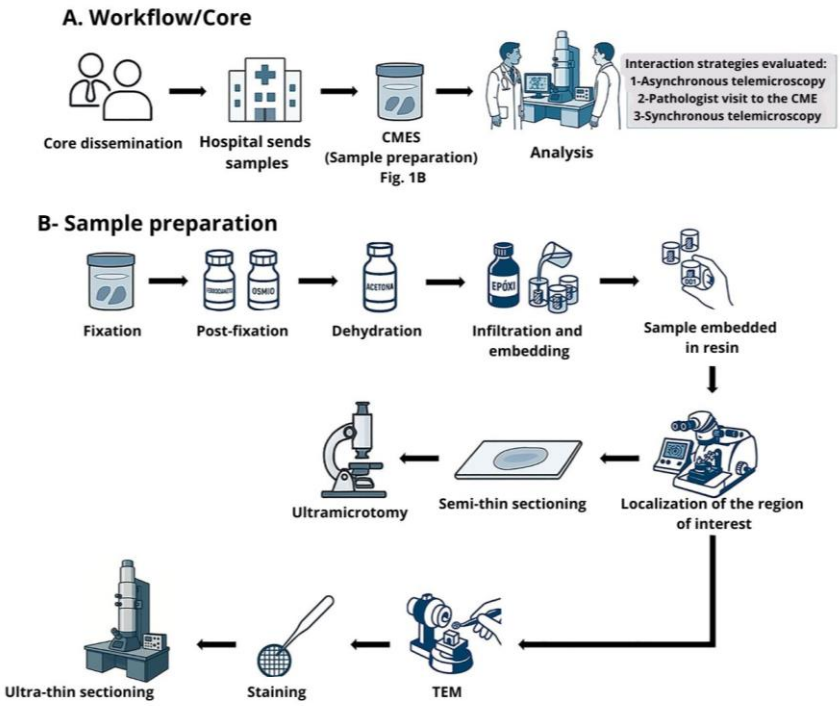
METHODOLGY

The definition of a structured and efficient workflow is one of the main factors for the consolidation of telemicroscopy as an effective diagnostic tool (Figure 1). To this end, methodologies based on protocols from international reference centers were adopted, notably the Department of Cellular Pathology at the University of Manchester and the Histopathology Unit of the Gulbenkian Institute of Molecular Medicine in Portugal, for the reception and categorization of samples. These protocols guided the structuring of the workflow, which was subsequently adapted to the specific characteristics of the national center involved, the National Center for Structural Biology and Bioimaging (CENABIO, UFRJ).

After implementing the workflow, we tested three interaction strategies between the electron microscopy centers (EMCs) and hospitals: synchronous and asynchronous telemicroscopy, and an in-person visit of the pathologist to the EMC. In asynchronous telemicroscopy, images were acquired by a specialist and were available in databases to the pathologist. In synchronous telemicroscopy, the pathologist had remote access to the microscope via a screen-sharing tool and guided the imaging performed by the specialist. In the third strategy, the pathologist went to the EMC and participated in person in the image acquisition. To test these strategies, samples from three patients with renal pathologies were selected, with each sample being sent for evaluation using one of the strategies.

The images obtained were stored in a digital database and will be used later for the development of artificial intelligence (AI) software that optimizes differential diagnosis through TEM.

Figure 1: Schematic of the workflow and sample preparation for transmission electron



(A) The established workflow stipulates that, after sample collection, the pathologist sends the samples to the CME (Central Microscopy Unit). This shipment may consist of samples that have already been processed or samples to be processed by the CME team. The interaction models between the CME and pathologists evaluated include synchronous or asynchronous telemicroscopy, in addition to the pathologist's in-person visit to the CME. (B) Sample processing includes the steps of fixation, post-fixation, dehydration, infiltration, and embedding, resulting in the sample embedded in resin, from which ultrathin sections are made, which will be stained and evaluated using TEM (Transmission Electron Microscopy). An intermediate step necessary for some pathologies is the preparation of semi-thin sections evaluated by light microscopy to verify the presence of the region of interest. If negative, new semi-thin sections can be made until the ideal region for verifying pathological changes is reached.

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RESULTS

To maximize sample acquisition and attract collaborating pathologists, audiovisual promotional material for the core facility was produced. The video demonstrates how hospitals can connect CME (Continuing Medical Education) centers, enabling doctors to access sophisticated, state-of-the-art equipment capable of facilitating differential and remote diagnosis within the telemicroscopy network. Currently, we have the participation of collaborating pathologists affiliated with partner hospitals, including the Clementino Fraga Filho University Hospital, the Pedro Ernesto University Hospital, the Paulo Niemeyer State Brain Institute, and the Alfredo da Matta Hospital Foundation. Physical proximity in these cases was important to facilitate in-person visits and evaluate interaction strategies between the teams. However, once implemented, this operating model will be entirely based on telemicroscopy and can be adapted to other hospitals and microscopy centers in the country, possessing enormous potential for expansion.

During this initial period of implementing the telemicroscopy core facility, the CME received samples from 9 pathologies: Ciliary Dyskinesia, PIT1 Pituitary Adenoma, Thrombotic Microangiopathy, Membranous Glomerulonephritis, Rapidly Progressive Glomerulonephritis, Focal Segmental Glomerulosclerosis (FSGS), Minimal Change Nephrotic Syndrome, Crohn's Disease, and Leprosy. All samples were selected for evaluation of the optimal workflow and for assessments of sample processing and identification of regions of interest. Among the received pathologies, FSGS samples were used for comparative evaluation of the interaction strategies.

Upon receipt, each sample was identified by a unique code containing the sample entry number and the associated pathology abbreviation. Other information included in a spreadsheet shared between the CME and the pathologists included the identification of the sample's originating institution and the responsible pathologist, the tissue type, the diagnostic hypothesis, the sample entry date, and the person responsible for receiving it at the CME, in addition to the sample preparation data.

The main key to successful analysis in electron microscopy lies in the proper processing or preparation of the sample (Fig. 1B), respecting the specificities and objectives of the analysis in the context of each pathology. For this, good communication between the electron microscopy team and the pathologists is crucial from the beginning of the interaction, sharing information such as the type of tissue, diagnostic hypothesis, ideal fixation and staining solutions, and the expected ultrastructural details. The quality and intensity of this communication and interaction have proven to be determining factors for the fluidity of the workflow and the speed of differential diagnosis. It is advisable to establish an open channel of interaction, for example, through the use of current technologies such as frequent online video conferences and messaging applications that allow for faster interaction, including the formation of groups, facilitating contact between team members at different stages of sample processing and analysis.

Once the interaction is established, it is important that the CME (Central Medical Equipment) team guides how to proceed with the collection and fixation of the material, supplying the reagents and the protocol for the fixative solution, or providing the solution already prepared. This ensures that the material is fixed immediately after collection. Some hospitals and medical institutions, especially university hospitals, have their ultrastructural pathology departments, enabling part of the sample preparation to be done by on-site personnel. However, we have observed that material prepared entirely by the CME team tends to show greater reproducibility, enabling the rapid detection and standardization of diagnostic characteristics.

Another stage where the interaction between the CME and the pathologists proved fundamental was in determining the region of interest in the resin blocks containing the processed sample. For this purpose, for samples of some tissues, such as renal tissue, the preparation of semi-thin sections, observed by light microscopy, was implemented before the preparation of the ultra-thin sections evaluated by TEM (Fig. 1). After the completion of all sample preparation steps and/or the definition of the region of interest, the analysis and imaging of the material in the TEM followed for the detection of the ultrastructural characteristics crucial for differential diagnosis. The acquisition was initially standardized according to the pathology under analysis, using defined magnifications, ensuring the quality and comparability of the obtained data.

Three interaction strategies between the teams were tested: synchronous telepathology, asynchronous telepathology, and in-person meetings. Synchronous telepathology allowed for real-time discussions between the pathologist and the imaging specialists. This direct communication enabled the confirmation of the presence of structures of interest and important diagnostic characteristics, resulting in faster final diagnoses and enhanced interdisciplinary collaboration. Both synchronous and in-person strategies facilitated the combination of the transmission electron microscopy (TEM) specialist's expertise in identifying ultrastructures with the pathologist's knowledge of pathology and the patient's clinical history. This collaboration ensured greater accuracy in image interpretation and reduced the time needed to reach a diagnosis. In contrast, asynchronous telepathology required two or more remote meetings between the pathologists and the TEM team to discuss the obtained images. This extended time frame was likely due to the complexity and specific ultrastructural diagnostic features of the pathology presented. Overall, considering the challenges of pathologists' time availability and the travel required to reach TEM centers, synchronous telepathology emerged as the most effective strategy at our telehealth center. It has the potential to democratize access to electron microscopy for differential diagnosis on a national level, benefiting multiple hospitals.

The generated database includes approximately 3,000 digital images of the analyzed pathologies, which are stored on shared drives. For better organization, the images have been categorized according to the sample entry number and the associated pathology. This systematic arrangement enables easy identification of images that contain the specific fragment and region of interest. It also facilitates integrated access for the teams at the participating centers, streamlining database management.

The proposed model demonstrates the effectiveness of integrating different national reference centers and the possibility of expanding access to ultrastructural diagnosis through telemicroscopy. The collaboration between the EMCs and hospital services contributes to the incorporation of high-resolution morphological analyses into routine diagnostic procedures, positively impacting the quality of pathological investigation, accuracy, and support for clinical decision-making.

DISCUSSION

Proper sample preparation is fundamental for the success of analyses in electron microscopy, especially when they are aimed at the ultrastructural diagnosis of human pathologies. The integrity of the results generated depends not only on the quality of the reagents and equipment, but also on the standardization of protocols and the technical competence of those who perform them[16]. For this reason, centralizing sample preparation in specialized centers, such as electron microscopy centers (EMCs), has proven highly effective, ensuring homogeneity, traceability, and reproducibility of the procedures.

However, technical excellence in diagnostics is only achieved when it is combined with integrated and continuous communication between the different professionals involved in the workflow. Dialogue between microscopy technicians and pathologists is essential from the very beginning, starting with sample collection and fixation, through processing, ultrathin sectioning, image acquisition, and finally, the final analysis. In all these stages, sharing clinical information, diagnostic hypotheses, and expected morphological criteria guides technical procedures and optimizes resources, avoiding waste of time and materials.

The unique nature of the pathologies examined through electron microscopy—often of uncertain origin, whether infectious, genetic, or degenerative—poses both challenges and opportunities. On one hand, there is a need for careful evaluation and specialized experience, which requires highly qualified professionals. On the other hand, certain ultrastructural alterations display distinctive morphological patterns that can help exclude differential diagnoses, playing a critical role in the diagnostic process for pathologists. Therefore, despite its complexity, electron microscopy provides unique opportunities for diagnostic clarification, particularly in complex or poorly understood cases.

Within this scenario, direct and constant contact with the pathologist throughout the entire workflow proves to be one of the greatest advantages of telemicroscopy. This proximity allows decisions to be made collaboratively, in real time, including during ultramicrotomy and imaging. The pathologist can guide the specialist in choosing the most representative region of the tissue, request additional sections, or indicate specific alterations of interest, avoiding repeated procedures and ensuring that the material is analyzed with maximum efficiency.

To ensure the efficiency of the process, it is essential to strategically select and train the appropriate professionals for each stage. In the initial phase, local healthcare teams must be trained to immediately fix samples in order to faithfully preserve the ultrastructure of the tissues. Delays in this step can lead to cellular degradation

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and the formation of artifacts, which can compromise the morphological analysis significantly. Having a team experienced in electron microscopy is crucial for processing the samples and adjusting microscope parameters to ensure the acquisition of high-quality images. In the final stage, pathologists interpret the data obtained, integrating it into the clinical context. Based on our experience at the telehealth center, we recommend that pathologists interested in using Transmission Electron Microscopy (TEM) receive training in ultrastructural analysis relevant to their medical specialty.

The distribution of tasks values the specific skills of each professional and contributes to the optimization of results. Supervision by a technical-scientific coordinator ensures the standardization of procedures and the traceability of analyses. In regions with limited resources, it is possible for the same professional to perform multiple functions; however, specialization in each stage is the ideal scenario to ensure the quality and efficiency of the process.

The implementation of the telemicroscopy core, currently under development, represents an important step towards establishing an ultrastructural diagnostic network in Brazil. This initiative offers strategic and structural benefits for the healthcare system, such as democratizing access to TEM (Transmission Electron Microscopy), which has historically been concentrated in the South and Southeast regions[15], reducing regional inequalities in high-complexity diagnostics, and consolidating a collaborative network among specialists from different institutions and states. The implementation of telemicroscopy can also contribute to reducing the environmental impact by decreasing the need for physical transportation of samples and professionals, resulting in lower CO_2 emissions associated with transport and in-person travel [20].

The consolidation of digital image databases and their respective reports creates a valuable resource for educational, scientific, and training purposes, allowing for the development of standardized atlases and diagnostic protocols. These databases also enable the training of AI algorithms, which could in the future assist in image screening, morphological pattern recognition, and suggesting differential diagnoses, optimizing analysis time and increasing diagnostic accuracy, especially in environments with a shortage of specialized pathologists [21].

Our research group also foresees, in its medium-to-long-term perspective, the incorporation of advanced three-dimensional microscopy techniques, which allow for the volumetric analysis of cellular structures with micrometric resolution and the observation of different cross-sectional planes. This approach, combined with the power of AI, can pave the way for a new era in diagnostic pathology, where subcellular alterations will not only be identified but also quantified and spatially contextualized with scientific rigor.

CONCLUSION

The integrated model of electron microscopy and telemicroscopy, developed at the center, proves to be an innovation for strengthening diagnostic pathology. The combination of rigorous technical preparation, interdisciplinary communication, the use of digital technologies, and continuous professional training creates the ideal conditions for accessible and rapid differential diagnosis. The expectation is that, with the consolidation of this model, Brazil can benefit from telemicroscopy in public health, transforming a historically restricted field into a widely available and strategic instrument for addressing complex and emerging diseases.

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