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CASE REPORT

Title: A Novel Case Report of CD5-Negative Mantle Cell Lymphoma Presenting in the Oral Cavity

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ABSTRACT

Proliferating lymphoid cells in lymphoma have the potential to involve not only lymph nodes, but other lymphoid tissues (including those in the oral cavity). This case represents a very rare diagnostic entity: oral extranodal presentation of CD5-negative Mantle cell lymphoma. In asymptomatic palatal swellings in adults, this uncommon variant of lymphoma should be considered in the differential diagnosis because early detection and treatment improve patient outcomes.

STATEMENT OF CLINICAL SIGNIFICANCE

CD5-negative mantle cell lymphoma (MCL) is an uncommon MCL variant. Early identification and treatment of MCL improves outcomes and prognosis. The differential diagnosis for palatal swelling should include CD5-negative MCL as a rare but distinct possibility. This case highlights the value of interdisciplinary collaboration for the diagnosis of such uncommon conditions.

KEYWORDS

Mantle Cell Lymphoma; Mouth Neoplasms; Head and Neck Cancer; Diagnostic Imaging; Immunohistochemistry

INTRODUCTION

Lymphoma represents a diverse group of malignant neoplasms characterized by abnormal proliferation of lymphoid cells [1]. Lymphoma is further subclassified into Hodgkin lymphoma and non-Hodgkin lymphoma, with the latter being approximately 90% of cases [1]. Non-Hodgkin lymphoma is further subdivided into 2 major subtypes, B-cell lymphoma which represents the vast majority with 90% of cases reported, and T-cell and natural killer (NK)-cell lymphoma

[1]. Each of the lymphoma categories is typically diagnosed through utilization of morphologic, immunohistochemistry, genetic, and molecular studies with correlation of clinical, radiologic, and other laboratory findings (e.g., serum protein electrophoresis, serum immunofixation electrophoresis, CBC, etc.) to allow precise diagnosis for the following patient management.

Mantle cell lymphoma (MCL) is a distinct rare subtype of B-cell non-Hodgkin lymphoma that is generally considered as an intermediate to aggressive form of CD5-positive B-cell malignancy with chromosomal translocation t(11;14) [1, 2]. MCL originates in the mantle cell zone of lymph nodes and is characterized by uncontrolled proliferation of CD5-positive B-cells [3]. MCL typically involves lymph nodes and is associated with swelling of lymph nodes (i.e., lymphadenopathy), fever, night sweats, and weight loss [2]. Less commonly, MCL is reported in extranodal sites including the gastrointestinal tract, conjunctiva, bone marrow, blood, and the submandibular salivary duct and oral cavity [4].

More recently, a subset of MCL that is CD5-negative has been identified in up to 10% of cases [5]. The lack of CD5 expression may improve survival in MCL patients independently of other favorable prognostic markers such as IgHV hypermutation, absence of SOX11 expression, low Ki-67 (a marker of proliferation), and kappa restriction [5].

MCL is rare, with an estimated incidence of 0.55 per 100,000/year (0.0006%) [6]. It is more common in men (male : female ratio = 4:1) [6]. The incidence of MCL increases with age peaking in the 6th and 7th decades [6]. Similar to our case, many cases of MCL are diagnosed late at stage III or IV disease [6, 7]. Extranodal involvement is a characteristic feature of late stage MCL, but quick identification and treatment have the potential to improve patient outcomes [8]. Therefore, although rare, it is important to be familiar with the clinical presentation of MCL so that it is diagnosed as early as possible.

The purpose of this article is to report on a case of CD5-negative MCL in the palate of a 77-year-old male. The clinical, microscopic, and immunophenotypic features of this lesion are presented together with review of the relevant literature.

CASE REPORT

The patient is a 77-year-old male who was referred to the oral medicine clinic for evaluation of an asymptomatic palatal swelling of unknown duration. The patient reported that he ate something previously that scraped the roof of his mouth, leaving behind the swelling. It had never been tender or painful and did not interfere with eating. The patient reported feeling well overall, and denied fever, night sweats, and unintentional weight loss.

His medical history was notable for hypertension controlled with lisinopril and carvedilol, and for multiple skin cancers (both basal cell and squamous cell carcinomas). Surgical history included right leg surgery for polio in childhood and Mohs surgery for skin cancers (multiple from 2000 to present day). No significant family history was reported. Social history included consuming 6 beers per day and no tobacco or recreational drug use.

On clinical examination, the patient demonstrated asymmetry of the hard palate (**Figure 1A and 1B**). The right posterior hard palate, just adjacent to the midline, had a slightly raised area that was soft and fluctuant on palpation with an overall purplish discoloration. This area was 1-1.5cm in diameter and nontender to palpation. The posterior left hard palate was also slightly soft to palpation with a more subtle purple discoloration but was neither raised nor fluctuant. The working diagnosis on examination was mucoepidermoid carcinoma, with concern for other minor salivary gland tumors such as pleomorphic adenoma. In-office imaging was completed and incisional biopsy was performed.

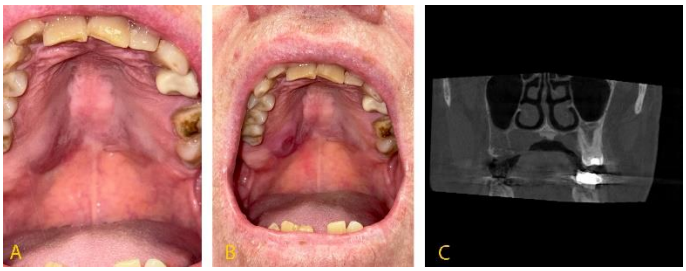

Figure 1. Clinical and imaging findings. Initial presentation (A) Approximately two weeks following biopsy (B). Initial CBCT imaging demonstrating soft tissue asymmetry on the right side (C)

Cone Beam Computed Tomography Imaging Findings

Cone Beam Computed Tomography (CBCT) was obtained to rule-out bone involvement. The radiographic findings from the posterior hard palate to the right of the midline noted more prominent gingival soft tissue on the right side extending from the right second molar to approximately the soft palate, which was consistent with the soft tissue lesion described clinically (**Figure 1C**). Possible pressure resorption was noted posterior to the second molar, and it was suggested that this finding may be related to pressure from the soft tissue lesion. The ridge crest at the site was concave and irregular in outline with two small radiolucencies present on the palatal aspect of the alveolus; otherwise, the alveolar bone was intact. The concavity was suggestive of normal anatomy and imaging suggested the irregular contour and radiolucencies may also represent normal anatomy, but the possibility of infiltration of the bone could not be ruled out. Due to the nondescript nature of the bony changes, clinical correlation was indicated to determine the extent of the lesion.

Pathology Reports

The preliminary diagnosis provided by histologic examination was atypical lymphoid infiltrate (**Figure 2**). Given the high suspicion for lymphoma based on the initial histopathologic findings, the specimen was submitted for hematopathology consultation and immunohistochemical evaluation. The final diagnosis was mantle cell lymphoma, CD5-negative. Specifically, morphologic examination of the biopsy revealed overlying benign squamous epithelium without dysplasia or involvement by the infiltrative process. Below the epithelium, some salivary glandular tissue was noted. The sample was predominated by lymphoid infiltrate, a densely packed cellular proliferation comprised of small monotonous lymphoid cells with hyperchromatic nuclei and conspicuous nucleoli and dense coarse chromatin (**Figure 2**). No readily visible mitotic figures or significant pleomorphism or tissue necrosis noted. The lymphoid cellular proliferation infiltrated the adjacent salivary parenchyma and surrounded ductal structures (**Figure 2**). No significant numbers of large atypical lymphoid cells were seen. No granuloma, malignant non hematopoietic cells, or Reed-Sternberg cells were seen. Proliferation centers were not noted. Initial findings raised suspicion for lymphoma, so a panel of immunohistochemical stains was performed including, Cyclin D1, SOX11, CD20, CD5, CD10, CD3, CD23 and Ki-67 for further evaluation. All positive and negative controls stained appropriately. The neoplastic lymphoid cells expressed CD20 (**Figure 3C**) with cyclin D1 (**Figure 3A**) and SOX11 (**Figure 3B**) without CD5 (**Figure 4B**). The infiltrate was negative for CD3, CD23, and CD10 (**Figures 4A, 4C, and 4D**). Ki-67 was positive in a minor subset of the lymphoid cells (<30%), consistent with a low proliferation index (**Figure 3D**). The morphologic features and histochemical findings are consistent with a CD5-negative small cell lymphoma of B-call origin. Cyclin D1 overexpression is a hallmark of MCL, representing a key event for MCL pathogenesis in the naïve pregerminal center B cells [9]. SOX11 overexpression is another

characteristic finding of MCL as it drives oncogenesis through a regulatory pathway that inhibits plasma cell differentiation [10]. Cyclin D1 and SOX11 overexpression are two critical findings that ruled out other CD5-negative small cell lymphomas of B-call origin, such as follicular lymphoma (CD5-negative, CD10-positive, cyclin D1-negative, SOX11-negative), CD5-negative small lymphocytic B-cell lymphoma (CD5-negative, CD23-positive, cyclin D1-negative, SOX11-negative), and marginal zone B-cell lymphoma (CD5-negative, CD10-negative, cyclin D1-negative, SOX11-negative) [10, 11]. These features were diagnostic of CD5-negative mantle cell lymphoma.

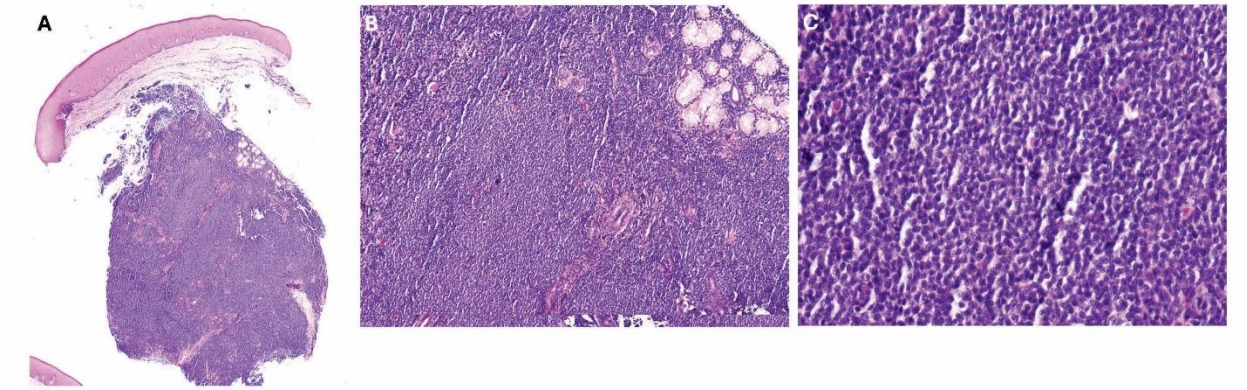

Figure 2. Microscopic Findings. Hematoxylin and eosin-stained sample demonstrating an atypical, monotonous lymphoid infiltrate comprised of small lymphocytes with condensed chromatin without proliferation centers or significant numbers of large lymphoid cells at 2X (A), 10X (B), and 40X (C) magnification.

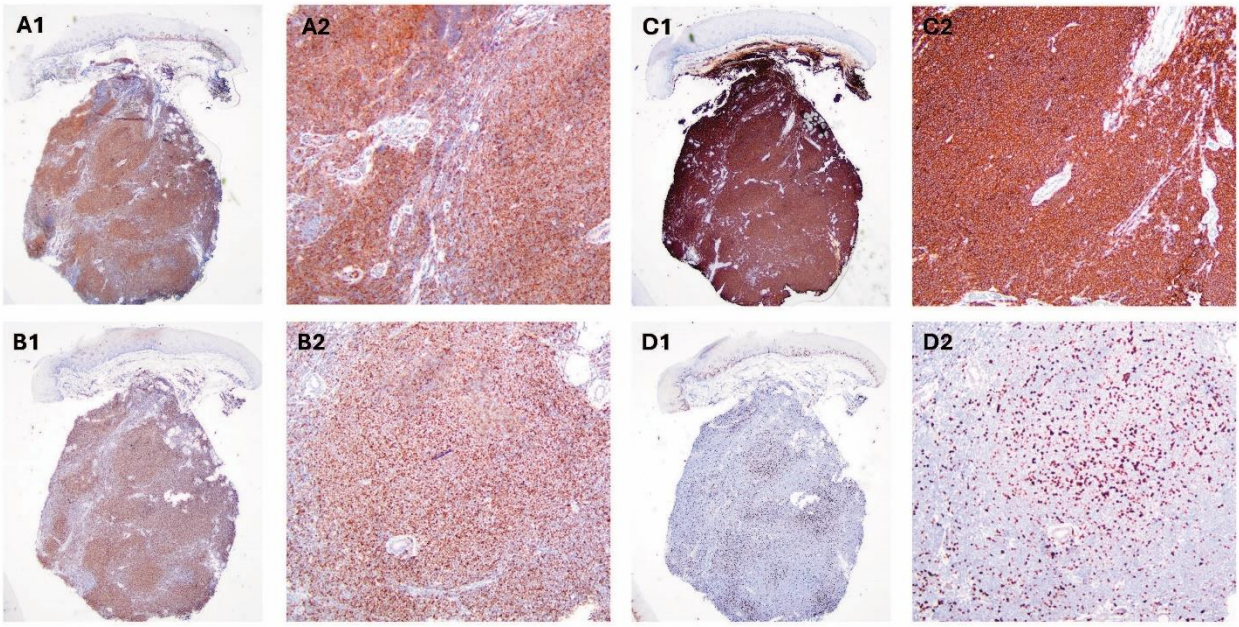

Figure 3. Positive Immunostaining Results. Panels show representative images for the positive immunostaining results. A. Cyclin D1 staining, which highlights lymphoma cells at 2X (1) and 4X (2) magnification; B. SOX11 staining, which highlights lymphoma cells at 2X (1) and 4X (2) magnification; C. CD20 staining, which highlights majority of lymphoma cells within nodular infiltrate at 2X (1) and 4X (2) magnification; D. Ki-67 staining, which highlights some lymphoma cells (overall <30%) at 2X (1) and 10X (2) magnification. The above immunostaining results are considered positive with a low proliferation index.

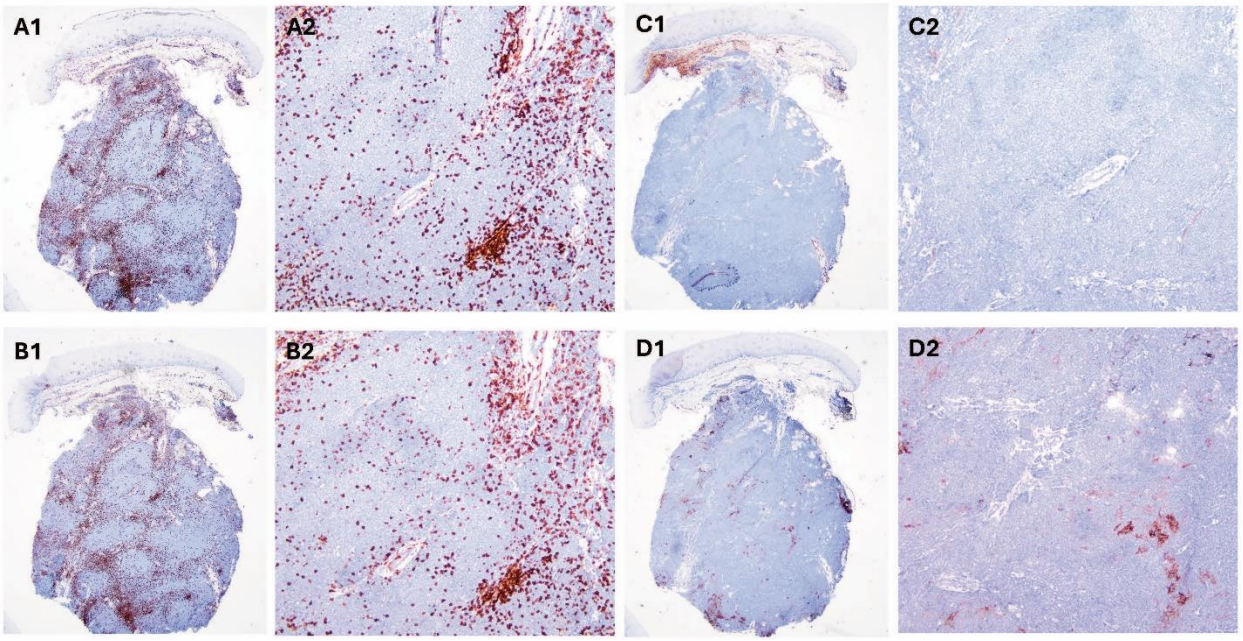

Figure 4. Negative Immunostaining Results. Panels show representative images for the negative immunostaining results. A. CD3 staining, which highlights a minority of lymphoid cells within nodular infiltrate at 2X (1) and 4X (2) magnification; B. CD5 staining, which highlights a minority of lymphoid cells within nodular infiltrate (i.e., which was similar to CD3 staining) without co-expression with CD20 at 2X (1) and 4X (2) magnification; C. CD10 staining, which is negative within lymphoma cells at 2X (1) and 4X (2) magnification; D. CD23 staining, which highlights some residual dendritic meshwork without significant staining of lymphoma cells at 2X (1) and 4X (2) magnification. The above immunostaining results are considered negative.

Oncology Treatment

Flow cytometry was positive for CD5-negative B cell clonal population. Post microscopic diagnosis of MCL, positron-emission tomography/computed tomography (PET/CT), from the skull to the thighs, was completed for disease staging. Increased uptake of

fluorodeoxyglucose (FDG) was noted at the site of the MCL of the hard palate (**Figure 5A, 5B, 5C, 5D**). Additionally, lymph node enlargement was demonstrated in multiple areas including the bilateral cervical lymph nodes (low level FDG activity; maximum standardized uptake value of 4.2), mediastinal and hilar lymph nodes (FDG avid), cardiophrenic angle lymph nodes (low-level FDG activity), bilateral axillary lymph nodes (FDG avid), porta hepatis region lymph nodes (maximum standardized uptake value of 4.3), and hypermetabolic ilioinguinal/pelvic lymph nodes (**Figure 5D, 5E, 5F, 5G**). Based on the PET/CT, lymphomatous involvement was confirmed with an overall Deauville score of 4 due to extensive hypermetabolic lymphadenopathy above and below the diaphragm. The patient remained asymptomatic through diagnostic testing and treatment planning and started chemotherapy with rituximab and acalabrutinib. Interval PET/CT following three months of chemotherapy demonstrates treatment response, with near complete anatomic and metabolic resolution of lymphadenopathy involving the cervical, mediastinal, intraperitoneal, and inguinal lymph nodes corresponding to overall Deauville score of 2. Focal hypermetabolic activity within the hard palate resolved, but with mild diffuse uptake remaining.

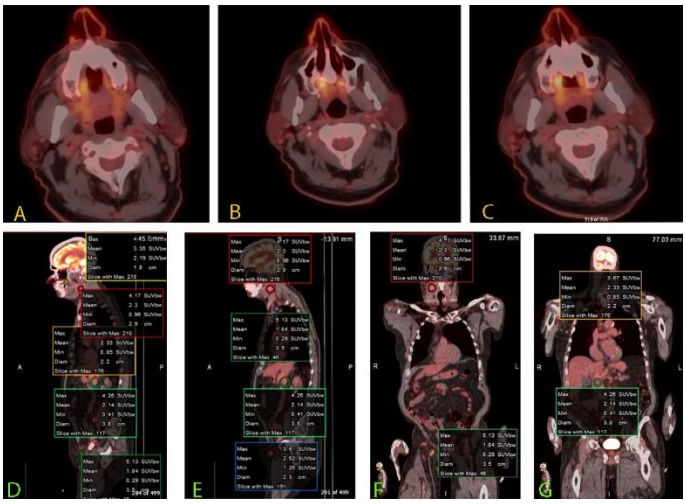

Figure 5. Positron-Emission Tomography/Computed Tomography (PET/CT) Findings. Axial slices demonstrating uptake within the lesion on the palate (A-C**).** Sagittal views demonstrate systemic involvement that was present at the time of diagnosis (D-G).

DISCUSSION

MCL is an uncommon B-cell lymphoma that accounts for 1.3% of all hematological malignancies and 6-10% of all non-Hodgkin lymphoma cases [12, 13]. The CD5-negative variant accounts for roughly 10% of MCL cases, meaning that it accounts for a remarkably small portion of all hematological malignancies [5]. A previous study using Surveillance Epidemiology and End Results (SEER) data found that MCL represents 7.8% of oropharyngeal hematologic malignancies, but this data does not capture oral cavity incidence [7]. Here, we report a case of an asymptomatic palatal lesion in a male patient that was diagnosed as CD5-negative MCL, discussed in the context of the literature.

A previous case series on head and neck mantle cell lymphomas by Carvolho et. al., 2023 found that 62.5% (10/16) cases were CD5-negative, which is higher than seen in earlier reports [14]. Of these CD5-negative cases, 3 were documented as painless while symptoms were not

specified for the remaining 7 cases [14]. Additional findings in the case series by Carvolho et al included ulceration in 1 case (no ulceration in 6 cases, not specified in 2 cases), absence of local bone destruction in 2 cases (not specified in 8 cases), and swelling in 8 cases (not specified in 2 cases) [14]. Three of the CD5-negative cases were hard palate lesions and 1 involved the upper lip and palate [14]. Although this finding suggests that CD5-negative cases may be more common in the hard palate, the true incidence of hard palate or even oral presentation of CD5-negative MCL is unknown [15]. Involvement of other sites was documented for 3 cases, 1 with peripheral blood involvement, 1 with lymph node involvement, and 1 with both [14]. Our case of an asymptomatic, non-ulcerated palatal swelling found to be CD5-negative MCL with peripheral blood and lymph node involvement shares similarities with the previously reported CD5-negative cases, but the comparison is complicated by data that is not specified in the prior case series [14].

The mechanism underpinning lack of CD5 expression in MCL is not well understood. It has been previously proposed that CD5-positivity may be gained as part of pathogenesis from *in situ* disease to MCL, but this does not account for the progression of CD5-negative *in situ* disease to CD5-negative MCL [16]. What has been demonstrated, though, are differences in disease outcomes. While MCL typically has an aggressive clinical course with a median survival of 3 to 5 years, CD5-negativity has been associated with more favorable overall survival independent of other prognostic factors (although this is based on reviews of relatively small retrospective case series) [5, 16]. Conventional MCL treatments previously relied heavily on intensive chemotherapy-immunotherapy or stem-cell transplant (SCT), but chemotherapy-related toxicities, new-onset second cancers, therapy related myelodysplasia, and myelosuppression/infection risk are all major concerns especially when treating an elderly patient population [2].

More recently, evolving MCL treatment options include non-chemotherapy targeted therapies like Bruton's tyrosine kinase (BTK) inhibitors (ibrutinib, acalabrutinib) in combination with anti-CD20 monoclonal antibodies, as used in this case [2]. Though some clinical practice guidelines for conventional MCL have been developed, treatments specific to CD5-negative MCL are not available [17]. Even in the absence of disease specific therapies, we show here a CD5-negative case that responded well to combined BTK-inhibitor and anti-CD20 monoclonal antibody administration. A prior case series comparing the outcomes of 58 CD5-negative and 212 conventional MCL cases noted that CD5-negative cases demonstrate longer progression-free survival than conventional MCL when both are treated similarly [15]. Importantly, emerging evidence suggests that earlier diagnosis and timely initiation of therapy are associated with improved clinical outcomes and overall prognosis in MCL, underscoring the importance of prompt recognition and management [18, 19].

CD5-negative MCL is associated with an improved prognosis relative to conventional CD5-positive disease; nonetheless, early detection remains important for timely treatment [5, 12, 13]. For uncommon diagnoses, timing of treatment, presence of systemic symptoms, and other patient factors may impact overall prognosis. This report shows that CD5-negative MCL should be considered in the differential diagnosis of asymptomatic palatal swellings in adults and illustrates the value of interdisciplinary collaboration in diagnosis and management of such cases.

CONCLUSION

In lymphoma, lymphoid cells may proliferate in lymphoid tissues other than lymph nodes. This case represents a highly uncommon diagnosis: oral extranodal presentation of CD5-negative MCL. CD5-negative MCL is associated with an improved prognosis relative to conventional CD5-positive disease, but early detection remains important for timely treatment.

Although ultimately rare, CD5-negative MCL is a valuable consideration in the differential diagnosis for palatal swellings in adults.

STATEMENT OF INFORMED CONSENT

Informed consent was obtained from the patient.

Contributions

Madison Richards, DMD: Conceptualization, Writing Original Draft, Review and Editing, Visualization, Project Administration
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Disclosure Statement

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Ethics approval: Ethics approval was not required.

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