OROFACIAL GRANULOMATOSIS AND ORAL SYMPTOMS IN A SOUTH AUSTRALIAN PAEDIATRIC POPULATION WITH CROHN’S DISEASE

DOCTOR OF CLINICAL DENTISTRY (Paediatric Dentistry)

By

Evelyn Kar-Yun Yeung
B.D.S (Adelaide)

Department of Paediatric Dentistry

School of Dentistry

Faculty of Health Sciences

The University of Adelaide

South Australia

August 2012
Thesis Declaration

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University’s digital research repository, the Library catalogue, the Australasian Digital Theses Program (ADTP) and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Evelyn Kar-Yun Yeung

August 2012
Table of Contents

Thesis Declaration ............................................................................................................ ii
Table of Contents .......................................................................................................... iii
List of Abbreviations .................................................................................................... vii
List of Tables ................................................................................................................ viii

Chapter II .................................................................................................................... viii
Chapter III ................................................................................................................... ix
Chapter IV .................................................................................................................... ix

List of Figures ............................................................................................................... x

Chapter II ..................................................................................................................... x
Chapter III .................................................................................................................... x
Chapter IV .................................................................................................................... xi
Chapter V ...................................................................................................................... xi

Abstract ....................................................................................................................... xii
Acknowledgements .................................................................................................... xv

Thesis Format............................................................................................................... xvi

Chapter I ......................................................................................................................... 17
Introduction ................................................................................................................... 17

Chapter II ..................................................................................................................... 21
Literature Review ......................................................................................................... 21

II. A. OROFACIAL GRANULOMATOSIS ................................................................. 22
   II. A. 1. Definition, Natural History and Prevalence ........................................... 22
Epidemiology- adults, children .................................................................................. 25
   II. A. 2. Clinical features ........................................................................................ 28
   II. A. 3. Aetiology ................................................................................................... 37
   II. A. 4. Pathogenesis ............................................................................................. 42
<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. A. 5.</td>
<td>Investigations</td>
<td>43</td>
</tr>
<tr>
<td>II. A. 6.</td>
<td>Diagnosis</td>
<td>49</td>
</tr>
<tr>
<td>II. A. 7.</td>
<td>Management</td>
<td>51</td>
</tr>
<tr>
<td>Dietary therapy</td>
<td></td>
<td>52</td>
</tr>
<tr>
<td>Local measures</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>Intrallesional therapy</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>Surgical therapy</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>II. B.</td>
<td>INFLAMMATORY BOWEL DISEASE</td>
<td>57</td>
</tr>
<tr>
<td>II. B. 1.</td>
<td>Definition and Epidemiology</td>
<td>57</td>
</tr>
<tr>
<td>II. B. 2.</td>
<td>Classification and Disease Activity Index</td>
<td>62</td>
</tr>
<tr>
<td>II. B. 3.</td>
<td>Crohn’s Disease Characteristics</td>
<td>65</td>
</tr>
<tr>
<td>II. B. 4.</td>
<td>Aetiology and Pathogenesis</td>
<td>73</td>
</tr>
<tr>
<td>Genetic and Immunological Factors</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Microbial</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Environmental</td>
<td></td>
<td>78</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>II. B. 5.</td>
<td>Investigations and Results</td>
<td>80</td>
</tr>
<tr>
<td>Oral Crohn’s Disease</td>
<td></td>
<td>83</td>
</tr>
<tr>
<td>II. B. 6.</td>
<td>Histopathology</td>
<td>85</td>
</tr>
<tr>
<td>General Histology</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>Oral Crohn’s Disease</td>
<td></td>
<td>88</td>
</tr>
<tr>
<td>II. B. 7.</td>
<td>Management</td>
<td>88</td>
</tr>
<tr>
<td>Active Disease</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td>Maintenance Therapy</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>Surgical Therapy</td>
<td></td>
<td>91</td>
</tr>
</tbody>
</table>
Complications .................................................................................................................91

IV. Association between Orofacial Granulomatosis and Crohn’s Disease .........................94

CONCLUSION ..................................................................................................................97

Chapter III ..................................................................................................................99

Article 1 (Scientific Article) ..........................................................................................99

Abstract ......................................................................................................................101

Introduction ................................................................................................................102

Methods ......................................................................................................................104

Results .........................................................................................................................106

Discussion ..................................................................................................................113

Conclusion ..................................................................................................................119

Chapter IV ..................................................................................................................120

Article 2 (Scientific Article) ..........................................................................................120

Abstract ......................................................................................................................122

Introduction ................................................................................................................123

Materials & Methods ...............................................................................................125

Results .........................................................................................................................126

Discussion ..................................................................................................................132

Chapter V ....................................................................................................................137

Article 3 (Case Report) ...............................................................................................137

Abstract ......................................................................................................................139

Introduction ................................................................................................................139

Patient 1 .........................................................................................................................140

Patient 2 .........................................................................................................................148

Discussion ..................................................................................................................157

Chapter VI ..................................................................................................................161

Discussion ..................................................................................................................161

The following methodological short comings were encountered in this study: .............165
This study included the following strengths: ..............................................................166

The implications of this study are that: ...............................................................166

Future research directions following this pilot study include: ..............................167

Chapter VII ........................................................................................................168

Conclusion ........................................................................................................168

Appendices .........................................................................................................170

*Women’s and Children’s Human Ethics Approval Letter* ..................................171

*Specific Questions for Crohn’s Disease* .........................................................176

*Oral health assessment form from the Oral Health Surveys (World Health Organisation (Geneva, 1997)* .................................................................179

*OFG/Oral Manifestations Disease Activity Index* ...........................................183

*Guide: Standardised views for clinical extra and intra oral imaging* ................186

*Orofacial Granulomatosis/Oral Crohn’s Disease Diagnostic Guide* ..............188

*Letter of invitation for participation* .................................................................192

*Information sheet for participants* ................................................................. 193

*Consent form for participation* ................................................................. 195

*Summary of oral histopathological features in each patient* .........................197

*Summary of significant GI lesions histological features identified in each patient* 199

References ...........................................................................................................201
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>APAIBDD</td>
<td>Australian Paediatric and Adolescent Inflammatory Bowel Disease Database</td>
</tr>
<tr>
<td>ASCA</td>
<td><em>anti-Saccharomyces cerevisiae</em> antibodies</td>
</tr>
<tr>
<td>CD</td>
<td>Crohn’s disease</td>
</tr>
<tr>
<td>CDAI</td>
<td>Crohn’s Disease Activity Index</td>
</tr>
<tr>
<td>CG</td>
<td>Cheilitis granulomatosa of Miescher</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>MRS</td>
<td>Melkersson Rosenthal syndrome</td>
</tr>
<tr>
<td>OCD</td>
<td>Oral Crohn’s disease</td>
</tr>
<tr>
<td>OFG</td>
<td>Orofacial granulomatosis</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>Perinuclear-staining antineutrophil cytoplasmic antibodies</td>
</tr>
<tr>
<td>PDU</td>
<td>Paediatric Dental Unit</td>
</tr>
<tr>
<td>WCH</td>
<td>Women’s and Children’s Hospital, Adelaide, South Australia</td>
</tr>
</tbody>
</table>
# List of Tables

**Chapter II**

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 1</td>
<td>Summary of conditions with orofacial swelling, their prevalence and year of publication</td>
<td>28</td>
</tr>
<tr>
<td>Table 2</td>
<td>Summary of clinical features of orofacial granulomatosis</td>
<td>30</td>
</tr>
<tr>
<td>Table 3</td>
<td>Possible clinical gastroenterology results of OFG and similar disorders</td>
<td>45</td>
</tr>
<tr>
<td>Table 4</td>
<td>Possible haematology and serology results of OFG and similar disorders</td>
<td>46</td>
</tr>
<tr>
<td>Table 5</td>
<td>Possible chest radiography results of OFG and similar disorders</td>
<td>48</td>
</tr>
<tr>
<td>Table 6</td>
<td>Possible patch testing results of OFG and similar disorders</td>
<td>49</td>
</tr>
<tr>
<td>Table 7</td>
<td>Differential diagnosis of OFG based on clinical presentation</td>
<td>50</td>
</tr>
<tr>
<td>Table 8</td>
<td>Possible histopathology results of OFG and similar disorders</td>
<td>51</td>
</tr>
<tr>
<td>Table 9</td>
<td>Incidence of CD in children and adolescents per 100,000 children per year</td>
<td>60</td>
</tr>
<tr>
<td>Table 10</td>
<td>Male preponderance in paediatric CD compared to adult CD</td>
<td>62</td>
</tr>
<tr>
<td>Table 11</td>
<td>Summary of revised ‘Montreal classification’ of Crohn’s disease</td>
<td>63</td>
</tr>
<tr>
<td>Table 12</td>
<td>Higher ileocolonic disease prevalence in paediatric CD compared to adult CD</td>
<td>68</td>
</tr>
<tr>
<td>Table 13</td>
<td>CD phenotype demonstrates progression of disease from inflammatory to structuring and penetrating disease</td>
<td>69</td>
</tr>
<tr>
<td>Table 14</td>
<td>Differences in Phenotypic and Natural History Characteristics of Paediatric- and Adult-Onset IBD</td>
<td>73</td>
</tr>
</tbody>
</table>
Chapter III

Table 1  Summary of reported gastrointestinal symptoms  109
Table 2  Summary of clinical extra and intra oral findings  112
Table 3  Frequency of extra and intra oral symptoms  113
Table 4  Reported outcome of the oral signs and symptoms following CD therapy  113
Table 5  Summary of clinical features of orofacial granulomatosis  117

Chapter IV

Table 1  Summary of the current clinical and histopathological diagnostic criteria for OFG and CD  124
Table 2  Summary of sites diagnosed as OFG  129
Table 3  Summary of oral and GI diagnosis (histological)  131
Table 4  Reported orofacial and GI clinical summary  132
Table 5  Summary of oral and gastrointestinal diagnosis based on combined clinical, serological and histological findings  133
List of Figures

Chapter II

Figure 1  OFG and its relationship to other noncaseating granulomatous conditions  26
Figure 2a  Cheilitis granulomatous crusting of the upper and lower lip with angular cheilitis  31
Figure 2b  Cheilitis granulomatous with induration of the upper lip  32
Figure 3  Linear mucosal ulceration  33
Figure 4  Gingival enlargement in OFG  34
Figure 5  Cobblestoned buccal mucosa  34
Figure 6  Mucosal tag in labial vestibule  35
Figure 7  Tongue fissure  36
Figure 8  Erythematous perioral swelling  37
Figure 9  Complex interplay between initiator and host cellular response resulting in granuloma formation  44
Figure 10  Paediatric Crohn’s Disease Activity Index  65
Figure 11  Model of intestinal chronic inflammation caused by errors of macrophages in patients with CD  78
Figure 12  Crohn’s disease as an immune deficiency  79

Chapter III

Figure 1  Frequency of reported extra oral symptoms  110
Figure 2  Frequency of reported intra oral symptoms  111
Chapter IV

Figure 1  Buccal mucosa biopsy specimen showing dermal infiltration, dense inflammatory cells and scattered granulomata 128
Figure 2  Lower lip biopsy specimen showing dermal infiltration with multinucleated giant cells and scattered granulomata 129

Chapter V

Figure 1a  Patient 1- Facial view of the swelling of the upper lip with fissuring and perioral erythema 142
Figure 1b  Patient 1- intra oral view of the mandibular labial granulomatous gingiva 143
Figure 2a  Lower lip biopsy specimen viewed at x10 magnification showing dermal infiltration with multinucleated giant cells and scattered granulomata 144
Figure 2b  Buccal mucosa biopsy specimen viewed at x20 magnification showing dermal infiltration, dense inflammatory cells and scattered granulomata 145
Figure 3a  Patient 1 with significant upper lip cheilitis granulomatosis prior to intralesional therapy 146
Figure 3b  Patient 1 undergoing administration of intralesional Triamcinolone under general anaesthesia 147
Figure 4a  Patient 1: 3 years post-treatment showing resolution of upper lip cheilitis granulomatosis and reduced gingival and mucosal erythema and granulomatosis 148
Figure 4b  Patient 2 with asymmetrical enlargement of the both the upper and lower lips with fissuring, angular cheilitis, and perioral erythema 150
Figure 5a, 5b  Patient 2 with a peri-anal tag 152
Figure 6  Patient 2 with a peri-anal tag 152
| Figure 6a | Buccal mucosal specimen at x10 magnification with non-specific granulomas and inflammation | 153 |
| Figure 6b | Lip biopsy specimen at x20 magnification with sub-epithelial non-specific inflammation and no granulomata present | 154 |
| Figure 7a | Patient 2 at the time of presentation with upper lip enlargement and fissuring, angular cheilitis and perioral erythema | 156 |
| Figure 7b | Patient 2 with significant erythematous anterior gingival and mucosal with an atypical appearance | 157 |
Abstract

This research is a pilot study to determine if oral manifestations, including orofacial granulomatosis (OFG) are a precursor to, or an oral manifestation of paediatric Crohn’s Disease (CD), or a separate pathological condition in a South Australian paediatric population. Additionally the investigation and management of two paediatric patients who first presented with oral symptoms and diagnosed with CD is reported.

Retrospective analysis was conducted on patients on the Australian Paediatric and Adolescent Inflammatory Bowel Disease Database and the medical records of patients with CD or OFG from the Paediatric Dental Unit, Women’s and Children’s Hospital (n=945). From this group, a cohort of 22 eligible South Australian paediatric patients participated in a prospective clinical study. Over a period of 14 months questionnaires and clinical assessments were conducted. Data collection included patient/parent questionnaire, clinical examination, clinical photography and serological investigation. Of the cohort of 22 paediatric patients with CD assessed, 54.5% of patients presented with oral involvement. The mean age of CD diagnosis was 11 years and 4 months, while the mean age of OFG diagnosis was 9 years and 6 months.

A retrospective analysis was conducted of oral and gastrointestinal biopsies from 8 paediatric patients who had had a provisional diagnosis of OFG and for whom subsequent investigation for CD was undertaken. The histopathological features of oral and gastrointestinal lesions in each patient were compared. Of the 8 patients assessed, 6 were diagnosed with OFG on the basis of the oral biopsies. Only 1 patient had both macroscopic and microscopic changes consistent with active CD and all 6 patients with OFG had perianal disease. A
multidisciplinary approach to investigating all relevant clinical, histological and serological information resulted in 7 of the 8 patients having a final diagnosis of CD.

The results from this study indicate that oral involvement maybe more common than the national data indicates and that it may both precede and be an oral manifestation of CD. From the histological investigation of oral and gastrointestinal biopsies there is no conclusive evidence found linking OFG and CD, however given the strong association between the two conditions and other clinical and serological markers, multidisciplinary management is recommended to establish a definitive diagnosis. Data obtained from the prospective clinical assessment and clinical photography was used to devise a visual OFG/oral CD diagnostic guide. This was developed to aid in the diagnosis of OFG and oral CD by medical and dental practitioners. The results from this study also indicate the importance of collaboration of dental and medical physicians to aid in early diagnosis and management of CD.
Acknowledgements

I would like to thank the following people for their support during my program.

A/Professor Sumant Gue, Head of Department in Paediatric Dentistry, The University of Adelaide and Women’s and Children’s Hospital for his expert opinion, advice, clinical teaching and time.

Dr David Moore, Head of Department (Gastroenterology), Women’s and Children’s Hospital, for his expert opinion, assistance and time.

A/Professor Richard Logan, Head, Discipline of Oral Diagnostic Sciences The University of Adelaide, for his expert opinion, support, encouragement and assistance.

Professor Alastair Goss, Oral and Maxillofacial Unit, The University of Adelaide, for his expert opinion, encouragement and time.

Drs Lynette Moore and Nick Manton, Head of Department and Consultant, Department of Pathology, Women’s and Children’s Hospital, for their time, assistance and opinions.

Department of Digital Media, Women’s and Children’s Hospital, for their time and expert clinical photography.

Dr Wendy Cheung, Consultant (Paediatric Dentistry), Women’s and Children’s Hospital, for her support and assistance.

My family, colleagues and friends for their ongoing support, assistance, encouragement and motivation throughout my course.
Thesis Format

This thesis presents the three different investigations in this study un-formatted articles which are intended for publication following submission of this thesis. Each article is presented individual chapters.

The introductory chapter discusses the background of OFG and CD, the null hypothesis, objectives of this research, specific aims and the link between the different investigations undertaken in this study.

The second chapter reviews the literature of OFG and CD to discuss the aetiology, clinical presentation, investigation, histopathology, and clinical management of CD and OFG.

The third chapter describes the main investigation from this study involving retrospective analysis of data and findings from questionnaires and clinical assessments.

The fourth chapter details the findings from the retrospective histopathological analysis of oral and GI biopsy specimens in 8 patients.

The fifth chapter consists of a case report of two paediatric patients who initially presented with both orofacial and gastrointestinal symptoms. Multi-disciplinary investigations were undertaken and the management of the oral symptoms was reviewed.

The final chapter discussed the major finding from the three investigations and their significance, problems that were encountered and potential future research based on the findings in this study.

All references are listed at the end of the thesis, and tables and figures with their corresponding text are presented together where possible.