Rural and Remote Health
MEDLINE listed
ARHEN
FRAME
ISSN 1445-6354
The International Electronic Journal of Rural and Remote Health Research, Education, Practice and Policy

CLINICAL CASE REPORT

Challenges in the diagnosis and management of Lynch Syndrome in an Indigenous family living in a remote West Australian community

L Schofield[1], J Goldblatt[1], B Iacopetta[2]

[1]*Genetic Services of Western Australia, Familial Cancer Program, Perth, Western Australia, Australia*

[2]*Molecular Oncology, School of Surgery, University of Western Australia, Perth, Western Australia, Australia*

Submitted: *14 June 2011;* ***Revised:*** *19 October 2011;* ***Published:*** *22 December 2011*

Schofield L, Goldblatt J, Iacopetta B

Challenges in the diagnosis and management of Lynch Syndrome in an Indigenous family living in a remote West Australian community
Rural and Remote Health **11: 1836. (Online) 2011**

Available: http://www.rrh.org.au

ABSTRACT

Context: Lynch syndrome (LS), also referred to as hereditary non-polyposis colorectal cancer, is a familial cancer syndrome characterised by young age of onset of colorectal and other extra-colonic cancers. Most studies suggest that LS accounts for approximately 1% of all colorectal cancers (CRC). The identification of persons with a mutation for this syndrome is of major clinical importance because regular and life-long surveillance has been shown to improve their survival through early cancer detection. However, the identification of LS among CRC patients is a major challenge because there are no specific distinguishing clinical features. Clinical criteria based on family history of cancer and age of cancer diagnosis have been proposed. For various reasons, these are not well utilised and clinicians often fail to refer high-risk CRC patients for genetic assessment of LS. The low rate of referrals to the single, state-wide familial cancer program in Western Australia led to calls for a more sensitive and specific means of detecting LS cases. Virtually all tumours from LS patients are characterised by the molecular features of microsatellite instability (MSI) and loss of expression of mismatch repair proteins detected by immunohistochemistry (IHC). It was recently established that routine MSI and IHC testing in CRC patients aged under 60 years was an effective screening tool to identify previously unrecognized

LS cases. This approach has now become routine practice in Western Australia and has led to the identification of more than 20 new LS families, including the Indigenous family described in this report.

Issues: Population-based screening programs can identify individuals who may not be aware of their at-risk status, who may have little prior knowledge of their medical condition and who may have limited access to tertiary health services. This report describes some challenges met when following up a positive screening result for LS in an individual residing in a remote community more than 2000 km from the state's only Family Cancer Clinic. The challenges included finding the patient, arranging genetic counselling and testing, informing him of the result and providing advice regarding life-long surveillance. Also discussed are issues relating to management of the extended kindred in terms of cultural sensitivities, intra-familial communication and involvement of the local health providers, as well as the provision of genetic counselling, testing and surveillance services for patients living in remote regions. Prior to this study, there were no known Indigenous families with LS in Australia.

Lessons learned: The likelihood of finding hereditary cancer syndromes in Indigenous families living in remote communities is low. However, advances in modern diagnostic screening technologies will result in the identification of an increased number of at-risk individuals, some of whom will be from minority groups or from remote communities. Despite geographical isolation and cultural differences, hereditary cancer syndromes can be managed in individuals and families living in rural and remote areas. The key issues identified from this case are flexibility with standard clinical genetic protocols and the presence of a local medical practitioner who takes an active interest in delivery of the genetic testing and surveillance strategies.

Key words: colorectal cancer, gene testing, genetic counselling, health services, Indigenous Australians, Lynch syndrome, population screening.

Context

The familial cancer syndrome, known as Lynch syndrome (LS), is characterised by an early-age of onset of colorectal cancer (CRC) and is associated with an increased risk of endometrial and other extra-colonic cancers[1-3]. The identification of germline mutation carriers for LS is important because early and regular surveillance has been demonstrated to improve the survival of these individuals[4]. However, this is challenging due to the absence of specific clinical features that distinguish LS mutation carriers. Although sets of defined criteria based on age at diagnosis and family history of cancer have been proposed to help identify potential carriers[5,6], these have proven difficult to implement[7,8]. This has led to alternative, laboratory-based strategies that evaluate tumour-related features.

Almost all tumours from patients with LS are characterized by DNA microsatellite instability (MSI) and concurrent loss of expression of DNA mismatch repair proteins, as detected by immunohistochemistry (IHC). Large, retrospective MSI- and IHC-based screening studies were recently conducted to detect previously unrecognized cases of LS in the Western Australian population[9,10]. During the course of this research, a sigmoid CRC from a 41 year-old Indigenous male tested positive. This resulted in the discovery of LS in one large family and the identification of three other families whose pedigrees were suggestive of hereditary cancer syndromes. These families are of mixed ethnicity and they reside in a coastal community more than 2000 km from the state's only Family Cancer Clinic located in the Western Australian capital city of Perth.

This article describes the challenges involved in the follow up of a positive test result from a population-based screening program for LS when the affected case resides in a remote community with only limited access to tertiary health services.

Issues

In the initial hospital-based screening study published in 2004[9], 1044 colon tumours diagnosed from 1990 to 2000 by the West Australian state pathology service provider (PathWest) were assessed for MSI and for protein expression using IHC. All cases showing positive test results were traced and notified of the result by the Family Cancer Clinic of the Genetic Services of Western Australia (GSWA). Ethics approval for the project was granted by the Sir Charles Gairdner Hospital and the former Confidentiality of Health Information Committee of the Western Australian Department of Health.

The patient or a surviving family member was contacted and provided with verbal and written information about the meaning and family implications of the result, the availability of genetic counselling, and surveillance advice as described previously by this group[10]. The means of conveying the information was determined on an individual basis and in collaboration with the treating clinician or GP. Gene testing was offered to consenting adults. Post-test counselling was also provided, irrespective of the gene test result.

Index case: Mr X from Family A

Among the cases for follow up was a male (Mr X) whose advanced sigmoid tumour had been resected 11 years earlier when the patient was aged 41 years. Mr X's tumour was positive for both MSI and the IHC test. His ethnicity was not known but the surname indicated that he may have been an Indigenous person. Information obtained from the state public health database showed that Mr X underwent initial surgery in 1993 at a major metropolitan hospital but no further health entries were recorded after that year. Mr X and many others with the same distinctive surname were listed on the State Electoral Roll when follow up began in early 2004. With the assistance of the local Aboriginal Medical Service he was eventually traced to a location 2000 km north of Perth. His local GP agreed to communicate the MSI/IHC results to the patient. After much discussion regarding protocols for further genetic testing, the local GP agreed to a joint counselling session which included himself, the patient, and a clinical geneticist. In conjunction with the GP, a telehealth video conference was organized.

The GP had worked in the region for many years. He knew Mr X and was therefore well-positioned to determine the most culturally appropriate means of discussing complex cancer genetics with him. Two genetic counselling sessions are normally conducted prior to testing and, for practical and privacy reasons, these do not usually involve the GP. The GP suggested that two sessions would not be appropriate because of the difficulty in arranging transport. Normal pre-test protocols were changed to accommodate this and other suggestions. The telehealth session was conducted in a location familiar to the patient as a three-way conversation between the patient, his GP and a geneticist. The provision of information was consistent with the patient's health literacy. At the end of the session, the patient provided informed consent for germ-line testing to determine his LS status.

Consistent with the IHC screening result, germ-line testing found a pathogenic mutation in the *MSH2* gene. Mr X also gave consent for his family members to be contacted, advised of their risk status and offered genetic counselling. The GP initially believed subsequent genetic testing of other family members, referred to as predictive testing, could be arranged without referral to the state Family Cancer Clinic. After further discussion it was agreed that family members who requested testing would, in conjunction with the GP, receive group counselling via telehealth video-conferencing. Six members attended the subsequent GP-mediated family session.

The regional medical officer obtained a pedigree of Mr X's extended family (referred to here as Family A), which consisted of 10 siblings, nine of whom were still alive in 2004. At the time of initial contact, no other cancer cases had been reported in Family A. Mr X's mother (Mrs K), an Australian Aboriginal woman, was alive and well but Mr X's

father had died of an unconfirmed colon cancer aged mid-40s.

In view of the large distance involved, family members were counselled by telehealth conferencing of the availability of predictive testing and informed of the recommended surveillance and management options. It was agreed that results would be delivered by the local GP. To date, seven of the remaining eight siblings have been tested for the mutation and four were found to carry the family mutation. The untested sibling developed colon cancer at 37 years of age in 2007. His tumour tested positive for MSI and with IHC, hence this individual is likely to carry the Family A gene mutation. Since the initial round of predictive testing performed in 2005, only two of at least 8 children from the third generation of Family A and now aged over 18 years have been tested. Both were found to have the mutation associated with LS. At least a further 28 children currently under the age of 18 years are at risk of being carriers of this syndrome.

Although only three family members have so far been diagnosed with a cancer, approximately 50–80% of individuals who carry an *MSH2* gene mutation are likely to develop a colon cancer by the age of 70 years. Females with an *MSH2* gene mutation have a 25–60% chance and 4–12% chance of developing endometrial cancer and/or ovarian cancer, respectively, by the age of 70 years[11]. It is advantageous to be aware of mutation status as soon as possible so that regular surveillance may aid in the early detection of cancer when it is at a more easily treatable stage.

Because the remote West Australian region in question has no resident specialist endoscopist, all colonoscopies are undertaken by the resident general surgeon. Considering the potentially large number of family members who are at risk, the regional surgical service will be confronted with a significant additional workload of surveillance endoscopies. Fortunately, this family has a concerned local GP who has agreed to coordinate the surveillance and to encourage other family members to attend for genetic counselling.

Once the concept of familial cancers had been discussed within Family A, several partners of the family members alerted the Family Cancer Programme at GSWA to their own family histories of cancer, leading to the identification of a further three Indigenous families with histories suggestive of hereditary cancer syndromes. This includes a family with multiple CRCs suggestive of LS and another family with multiple cases of breast cancer suggestive of a familial breast cancer syndrome. Efforts continue to trace affected members of these three families for further genetic testing.

Lessons learned

Population screening for genetic disorders results in the identification of individuals who would not generally be aware of their prior at-risk status. They often have little knowledge of the condition for which they were screened. This has become particularly pertinent where modern pathological testing of surgical specimens can reveal findings that suggest a familial cancer syndrome. The management of an Indigenous family from a remote location and ascertained as being at risk of LS highlighted some of the difficulties associated with population screening for familial cancers.

The incidence of CRC among Indigenous individuals of both sexes is lower than that of non-Indigenous Western Australians[12,13]. Prior to the current study there were no known Indigenous LS families in the GSWA database and to the authors' knowledge none have been reported elsewhere in Australia. Almost two-thirds of Indigenous West Australians reside in non-metropolitan areas[14], with many living in remote communities that have very limited access to tertiary health services. Therefore the likelihood of finding Indigenous families with hereditary cancer syndromes is low when using clinical criteria alone. The case of Mr X described demonstrates how population-based screening using laboratory tests for MSI and IHC can lead to the identification of previously unknown LS families living in remote communities. This work also highlights some issues associated with offering a comprehensive and culturally appropriate

clinical genetic service for Indigenous people with family cancer syndromes.

The follow up of young CRC patients diagnosed with an MSI-positive tumour involves effective communication between the pathologist, surgeon, GP, patient and the family cancer service. This can often be difficult to coordinate for patients residing in metropolitan areas, but for an Indigenous patient living in a remote region it represents a special challenge. In these circumstances, some flexibility in standard clinical genetic protocols may be required. Moreover, notions of privacy and confidentiality in families living in isolated and remote communities may differ markedly from the standard Western culture. In this particular family, two of whom were health workers, most members lived in a township and had good medical knowledge. The lines of communication appeared to be open and many family members and other relatives were aware of who had been tested and, subsequently, who carried the family mutation.

Defining people by their culture or race may not be an accurate descriptor but it is important to recognise that culture cannot be ignored by providers of clinical health services. Based on the residential address for Mr X, it was assumed at the beginning of the search that his ethnic background was Indigenous Australian. However, a classification of 'Indigenous' does not provide sufficient information to plan a culturally appropriate strategy. For example, when follow up commenced it was not known whether it was acceptable for a white female to make direct contact with a male of Aboriginal or mixed ethnicity, or to discuss a family history that may include deceased persons. After enquiring about cultural and ethnic factors, the family and the GP stated that the issues generally associated with more traditional Indigenous families were not applicable to this family.

The challenges were compounded by the distance separating Mr X from the state's only Family Cancer Clinic. No written correspondence was sent to him directly because of the lack of a street address, and concerns regarding his literacy and state of health. Contact would not have been possible without the local medical officer who played a pivotal role in locating the patient and obtaining culturally appropriate pre-test counselling and informed consent. He also facilitated the telehealth conferencing between Mr X and GSWA and arranged transport for sample collection. Once consent for germ-line testing had been obtained, it was a further 4 weeks before Mr X presented for blood collection. In order to obtain a viable sample from residents of remote West Australian communities, transport for the patient to attend the local phlebotomy service must be arranged. Delivery of the sample to the Perth-based genetics laboratory must also be organized in such a way that it arrives within a set time-frame and in good condition.

After the gene mutation test result was obtained for Mr X, confirmation of the pedigree of Family A became important for the identification of individuals who were at risk of developing cancer. One of the major challenges encountered with this large family was to ensure the pedigree was complete. Another problem was that some individuals were known by more than one name, as may be the case in Indigenous communities. Follow up was also made difficult by the geographical isolation and the *laissez-faire* attitude of many family members. Although the mutation in Family A was identified in 2005, to date only two family members other than Mr X's siblings have presented for gene testing.

Life-long surveillance of mutation carriers is critical for early cancer detection and presents challenges even in metropolitan centres. Many non-metropolitan centres in Western Australia lack advanced healthcare facilities; long-term GPs and resident specialists and are therefore dependent on visiting clinicians to provide specialist services. Surveillance for hereditary cancer syndromes is best managed by a single coordinator with a long-term interest in the family. In addition, preventive healthcare in remote regions often assumes a lower priority than acute and chronic health issues. The key to effective management of Family A was the identification of a local GP who took an active interest in delivery of the genetic testing and surveillance strategies. Furthermore, a member of Family A was employed in the

local healthcare service and was pivotal for intra- and extra-familial communication.

Discussion with members of Family A revealed the gene mutation most likely originated from Mr X's father who had migrated from Singapore in his early twenties and died of unconfirmed CRC at a relatively young age. They also reported that relatives of the family who resided in that country had a high rate of cancer, although this has yet to be formally confirmed. Since discovery of the mutation, an endometrial cancer was identified in a 48 year old mutation carrier as a result of surveillance that had been initiated following a positive gene test result for this sibling. The only untested sibling in the second generation of Family A was diagnosed with an advanced CRC in 2007.

The other advantage of ascertaining Family A was that extended family members explored their own family histories following the genetic counselling sessions and increased awareness of familial cancer syndromes. This resulted in another three families being identified with histories suggestive of the presence of familial cancer syndromes.

Conclusion

Routine MSI and IHC laboratory screening of CRC specimens in the Western Australian population has led to the identification of LS in an Indigenous family from a remote part of this state. Family A had not been identified based on clinical criteria alone during the 11 year period since the diagnosis of Mr X's cancer.

Despite the relative isolation and cultural differences, hereditary cancer syndromes can be managed in individuals and families in rural and remote areas. The key issues identified are flexibility with standard clinical genetic protocols and the presence of a local medical practitioner who takes an active interest in delivery of the genetic testing and surveillance strategies. The experience of following up this family has highlighted some of the difficulties associated with providing a culturally appropriate clinical genetic service for Indigenous people with familial cancer syndromes.

Acknowledgements

The authors are indebted to members of the index family and members of other families, GPs, surgeons, pathologists, laboratory staff, clinical geneticists, genetic counsellors and medical students who assisted with this study.

References

1. Aaltonen L, Salovaara R, Kristo P, Canzian F, Hemminki K, Peltomaki P et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *New England Journal of Medicine* 1998; **338(21):** 1481-1487.

2. Lynch H. Herditary colon cancer. *New England Journal of Medicine* 2003; **348:** 919-932.

3. Watson P, Vasen H, Mecklin J-P, Bernstein I, Aarnio M, Järvinen H et al The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. *International Journal of Cancer* 2008; **123(2):** 444-449.

4. Vasen H, Abdirahman M, Brohet R, Langers A, Kleibeuker J, Van Kouwen et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. *Gastroenterology* 2010; **138(7):** 2300-2306.

5. Vasen H, Watson P, Mecklin JP, Lynch H. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. *Gastroenterology* 1999; **116(6):** 1453-1456.

6. Umar A, Boland C, Terdiman J, Syngal S, De La Chapelle A, Ruschoff J et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *Journal of the National Cancer Institute* 2004; **96(4):** 261-268.

7. Grover S, Tschoegl E, Russo L, Syngal S. Referral rates are low for genetic evaluation in patients meeting Bethesda guidelines for HNPCC. *Gastroenterology* 2003; **124(4Suppl1):** A547.

8. Grover S, Stoffel EM, Bussone L, Tschoegl E, Syngal S. Physician assessment of family cancer history and referral for genetic evaluation in colorectal cancer patients. *Clinical Gastroenterology and Hepatology* 2004; **2(9):** 813-819.

9. Chai S, Zeps N, Shearwood A, Grieu F, Charles A, Harvey J et al Screening for defective DNA mismatch repair in stages II and III colorectal cancer patients. *Clinical Gastroenterology and Hepatology* 2004; **2(11):** 1017-1025.

10. Schofield L, Watson N, Grieu F, Li W, Zeps N, Harvey J et al Population-based detection of Lynch syndrome in young colorectal cancer patients using microsatellite instability as the initial test. *International Journal of Cancer* 2009; **124:** 1097-1102.

11. Bonadona V, Bonaiti B, Olschwang S, Grandjouan S, Huiart L, Longy M et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch Syndrome. *JAMA* 2011; **305(22):** 2304-2310.

12. Thomson N, Irvine J. *A review of cancer among Aboriginal people in Western Australia*. Perth, WA: Cancer Council of Western Australia, 2001.

13. Australian Indigenous Health*InfoNet*. *Review of cancer among Indigenous peoples*. (Online) 2009. Available: http://www.healthinfonet.ecu.edu.au/chronic-conditions/cancer/reviews/our-review (Accessed 1 June 2011).

14. Australian Bureau of Statistics. *Population distribution, Aboriginal and Torres Strait Islander Australians*. Canberra, ACT: Commonwealth of Australia, 2006.