

Original research

Xanthomas seen on capsule endoscopy: What are they saying about your patient's health?

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Summary of article (160 characters)

This novel research investigated whether xanthomas identified during capsule endoscopy were associated with underlying lipid disorders, impaired glucose tolerance, or diabetes mellitus.

Keywords

xanthoma, small bowel, capsule endoscopy, hyperlipidaemia, diabetes mellitus

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1 **Abstract**

2

3 **Background:** There is long-standing evidence of an association between cutaneous
4 xanthomas and underlying lipid metabolism disorders, impaired glucose tolerance, secondary
5 hyperlipoproteinemia and diabetes mellitus. Since the advent of capsule endoscopy (CE),
6 substantial numbers of endoscopies have shown evidence of small bowel xanthomas. These
7 have unknown significance to the patient and, consequently, are not routinely reported when
8 identified. Our research is the first study to investigate the significance of small bowel
9 xanthomas identified on CE with underlying lipid disorders or diabetes mellitus.

10

11 **Methods:** 54 patients participated in this prospective cohort study. We recorded patients'
12 demographic details, medical history, medication list, height, weight, and waist
13 circumference measurements. A blood sample for fasting lipids, fasting glucose and HbA1c
14 was collected. A blinded gastroenterologist reported whether xanthomas were present and
15 quantified the number of xanthomas.

16

17 **Results:** 37% of participants had small bowel xanthomas visualised during CE. The presence
18 of xanthomas was associated with a previous diagnosis of hyperlipidaemia currently treated
19 with anti-lipid medication (IRR 4.43; 95%CI 1.32 to 14.9; p=0.048) and was also associated
20 with increasing units of alcohol consumption (IRR 1.91; 95%CI 1.32 to 2.78; p=0.0007).

21

22 **Conclusion:** This demonstrates an association between the presence of small bowel
23 xanthomas with hyperlipidaemia, mainly in patients with hyperlipidaemia controlled by
24 medication. We also detected an association between small bowel xanthomas and increased
25 alcohol intake. The presence of small bowel xanthomas might trigger lipid evaluation, in
26 future clinical practice.

1 Introduction

2
3 Xanthomas (also referred to as xanthomas) are fatty deposits comprised of well-defined
4 clusters of foamy lipid-laden histiocytes. They are characterised by a yellow-orange colour
5 and are commonly observed dermally as subcutaneous plaques or tendinous nodules [1].
6 There is long-standing evidence of an association between cutaneous xanthomas and
7 underlying lipid metabolism disorders, secondary hyperlipoproteinemia, impaired glucose
8 tolerance and diabetes mellitus [1-5].

9
10 In the gastrointestinal tract, xanthomas are more commonly reported in the gastric mucosa.
11 They are often small (1-2mm), single or multiple, yellow, orange, or white well-demarcated
12 sessile macules with irregular outlines [6]. They are believed to occur as a non-specific
13 response to various insults, either iatrogenic or spontaneous [7,8]. However, small bowel
14 xanthomas have rarely been described and are reported in only a handful of case reports,
15 presenting either as a localised or diffuse pattern [9]. They are usually incidental findings
16 [10]. As they are infrequently reported, the pathogenesis and significance of small bowel
17 xanthomas has yet to be fully elucidated.

18
19 Since 2001, capsule endoscopy (CE) has been used to visualise the small bowel [11]. CE is
20 non-invasive, wireless, safe, does not require sedation and provides reliable visualisation of
21 the small bowel mucosa. Commercially available capsule endoscopes are 24.5 mm to 27.9
22 mm in length and 10.8 mm to 13.0 mm in diameter [11]. The capsule contains a camera,
23 battery, LED lights and a transmitter. They are capable of transmitting approximately 2 to 6
24 images per second to a receiver worn externally by the patient [11]. The images are
25 subsequently uploaded into proprietary software for visualisation by a gastroenterologist. The
26 European Society of Gastrointestinal Endoscopy and the British Society of Gastroenterology
27 recommend CE as the first-line investigation of obscure gastrointestinal bleeding [12]. CE is
28 also indicated for the diagnosis and management of NSAID side effects, Crohn's disease,
29 malabsorptive syndromes such as coeliac disease, inherited polyposis syndromes, small
30 bowel transplant management and the detection of small bowel tumors [11-13]. Incidentally,
31 CE has enabled easier detection of the presence of xanthomas in the small bowel. As there
32 has been no evidence regarding the significance of these xanthomas, they are not routinely
33 recorded on the formal endoscopy report when identified.

34
35 Therefore this study is significant because it will provide the first evidence of an association
36 between the presence of small bowel xanthomas and metabolic disorders, which could further
37 implicate its pathogenesis. Our hypothesis is that small bowel xanthomas could be secondary
38 to lipid disorders and diabetes mellitus. If this is the case, detection of xanthomas during CE
39 may indicate a need to change reporting practices to ensure that general practitioners (GPs)
40 are notified of these findings.

1 **Methods**

3 *Participants and study design*

4 This prospective cohort study was conducted among patients attending the Day Procedure
5 Unit of a single regional hospital (Launceston General Hospital). Ethics approval for the
6 research was granted by the University of Tasmania Human Research Ethics Committee
7 (reference number H11823). The study was therefore performed in accordance with the
8 ethical standards laid down by the Declaration of Helsinki (2013).

9
10 Patients aged 18 years or older who attended for CE between 23 September 2011 and 2
11 December 2013 were invited to participate in the study. All study participants provided
12 written consent prior to recruitment.

14 *Data collection*

15 A member of the study team completed a data collection sheet for each participant and
16 collected a blood sample for fasting lipids, fasting glucose and HbA1c tests. The data
17 collection sheet included age, sex, body mass index, past medical history, co-morbidities and
18 current medications. This information was entered onto the study database along with the CE
19 results and pathology results.

20
21 During reporting of the CE, the gastroenterologist, who was blinded to the patient's history
22 and blood results, recorded whether xanthomas were present and quantified the number of
23 xanthomas. Patients were excluded from the study if they had incomplete findings due to
24 delay in the CE reaching the small bowel.

26 *Statistical analyses*

27 The clinical question being examined was whether xanthomas seen on CE occurred more
28 frequently in the presence of either diabetes mellitus or hypercholesterolaemia. If an
29 association was found, the presence of xanthomas in patients who had not been investigated
30 might indicate the need for testing for diabetes mellitus or hypercholesterolaemia. Testing
31 this association involved estimating the rate of occurrence of xanthomas in the different
32 disease groups (incidence rates), and comparing the rates in patients without those diseases
33 (incidence rate ratios). These estimations were performed using Poisson regression, which
34 either estimate the mean number of xanthomas per patient (if the count of xanthomas for each
35 patient was used as the outcome variable) or the proportion of patients with xanthomas (if the
36 presence or absence of xanthomas was used). The relative risk (in this case the incidence rate
37 ratios) of the different predictor conditions (e.g. the presence or absence of treated
38 hyperlipidaemia) were examined simultaneously by multivariate Poisson regression, in order
39 to remove the effects of confounding variables. In order to determine whether investigation of
40 patients found to have small bowel xanthomas on capsule endoscopy would yield a higher
41 diagnosis rate of uncontrolled hyperlipidaemia compared to random patient selection, the
42 patients were classified into four groups according to their lipid status: 1) no current lipid
43 abnormalities (total cholesterol (TC) <5.2 mmol/L) and not on medications (n=17); 2) no past
44 history of lipid abnormalities, but current raised lipids (TC ≥ 5.2 mmol/L) and not on
45 medications (n=10); 3) past diagnosis of lipid abnormalities and current raised lipids
46 (TC ≥ 5.2 mmol/L) and not on medications (n=3); and 4) past diagnosis of lipid abnormalities
47 on lipid-lowering medication, whatever the current lipid levels (n=24). The assumption here
48 is that doctors have decided that patients had sufficiently serious lipid abnormalities to justify
49 commencing lipid-lowering medication, whilst other patients had lesser degrees of lipid

1 abnormalities that were either not been detected in the past, or were not sufficiently serious to
2 justify lipid-lowering medications.

3

4 The association between the presence of small bowel xanthomas was estimated by calculating
5 the incidence rate ratio using multivariable Poisson regression (IRR; 95% confidence
6 intervals; p-values), with variables selected by backward stepwise regression from a list of
7 variables included in the final model (hyperlipidaemia as classified above and diabetes
8 mellitus status, presence of end-organ disease, and weekly alcohol intake) plus age, gender,
9 body mass index, family history of hyperlipidaemia, family history of diabetes mellitus,
10 cholesterol (total, LDL, HDL), log.triglycerides, log.fasting glucose and HbA1c percentage
11 which were not included.

12

13 All analyses were performed using Stata MP2 version 14.1 (StataCorp, College Station, Tx
14 USA).

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1 **Results**

2
3 A total of 55 patients were invited to participate and 54 consented that were included in the
4 study.

5
6 The most common indication for CE was recurrent iron deficiency anaemia (n=39) (Table 1).
7 Mean age was 65.0 years (SD 16.0) and there were equal numbers of men (n=27) and women
8 (n=27). 17 participants (31.5%) had a total cholesterol level of ≥ 5.2 mmol/L, 27 (50.0%) had
9 a history of hyperlipidaemia and 12 (22.2%) had diabetes mellitus. 20 participants (37.0%)
10 had small bowel xanthomas detected during CE.

11
12 Small bowel xanthomas were detected in 12 of the 27 (44.4%) participants with
13 hyperlipidaemia, 5 of the 12 (41.7%) participants with diabetes mellitus (either unmedicated
14 or medicated) and in 3 of the 9 (33.3%) participants with end-organ disease.

15
16 Preliminary analyses found that the presence of small bowel xanthomas was associated with a
17 prior diagnosis of hyperlipidaemia (IRR 2.86; 95% CI 1.14 to 7.18; p=0.025), but not to
18 current poor control of blood lipids (IRR 1.04; 95% CI 0.50 to 2.17; p>0.90).

19
20 The final multivariable regression model (Table 2) demonstrated that the risk of the presence
21 of xanthomas is raised (IRR 4.43; 95%CI 1.32 to 14.9; p=0.048) in patients with prior
22 diagnosis of hyperlipidaemia treated with lipid-lowering medication compared to no past or
23 current diagnosis of lipid abnormalities, after adjustment for diabetes status, presence of end-
24 organ disease and current alcohol intake. Alcohol intake as a continuous measure is
25 associated with increasing risk of xanthomas (IRR 1.91; 95%CI 1.32 to 2.78; p=0.0007).
26 Diabetes status does not appear to be related to the risk of presence of xanthomas.

1 **Discussion**

2
3 Our research provides the first evidence of an association between the presence of small
4 bowel xanthomas and hyperlipidaemia, even among patients with hyperlipidaemia controlled
5 by medication. We also detected an association between small bowel xanthomas and
6 increased alcohol intake. No association with diabetes mellitus was seen.
7

8 In patients with small bowel xanthomas, 70% had a prior diagnosis of hyperlipidaemia or had
9 a total cholesterol ≥ 5.2 mmol/L on the day of the capsule endoscopy. Interestingly, 44% of
10 these patients were already on lipid-lowering medications. The persistence of small bowel
11 xanthomas in patients with hyperlipidaemia on medication may suggest a slow rate of
12 xanthoma clearance even when lipid-lowering is adequate. Alternatively, it could indicate
13 that patients might have had even higher lipid levels prior to commencement of lipid
14 lowering medications resulting in the deposition and persistence of small bowel xanthomas.
15

16 The association between small bowel xanthomas and increased alcohol intake is consistent
17 with our understanding of the effects of alcohol in dysregulating lipid metabolism and
18 elevating triglycerides [14]. It has been shown that chronic alcohol intake delays the
19 clearance of triglycerol-rich lipoproteins and these abnormal chylomicron remnants then
20 affects the feedback regulation of cholesterol synthesis in hepatocytes, resulting in increased
21 secretion of triglycerol-rich lipoproteins by the liver [15]. This may result in deposition and
22 the formation of small bowel xanthomas.
23

24 When one or more xanthomas are seen during a CE examination, it may be appropriate to
25 report the occurrence of the observation to the GP. In this study, it appears that the GPs
26 looking after this group of patients had investigated them for hyperlipidaemias and managed
27 them appropriately. Nevertheless, in a less well-investigated population, an alert to the GP
28 may be appropriate.
29

30 The main limitation of the study was the small number of study participants due to the
31 relatively small catchment population in the area. A power calculation indicated that a sample
32 size of around 250 would be required to detect a 20% absolute difference between
33 comparator groups (30% vs 50%), with larger numbers required if smaller differences were
34 needed to be detected. The study period would have had to be extended considerably to
35 recruit this number of participants as the hospital, in which the study was conducted performs
36 only 30-40 CEs per year.
37

38 Strengths of the study include a single blinded gastroenterologist visualising the CE images,
39 thereby reducing the possibility of reporting bias and the collection of a blood sample at
40 recruitment for fasting lipids, fasting glucose and HbA1c tests, rather than relying on patient
41 records. Nevertheless, the lipid status of the patients was not fully characterised and
42 subgroups of lipid disorders may have been present that increased or decreased the likelihood
43 of presence of small bowel xanthomas in some patients.

1 **Conclusion**

2

3 In conclusion, our research provides the first evidence of an association between the presence
4 of small bowel xanthomas and hyperlipidaemia and increasing alcohol intake, even among
5 patients with hyperlipidaemia controlled by medication. This suggests that gastroenterologists
6 should notify GPs when xanthomas are detected during capsule endoscopies.

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4 The authors wish to thank the patients who participated in the research.

5

6 **Conflicts of interests**

7

8 None of the authors have conflicts of interest to declare.

9

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Table 1. Indication for capsule endoscopy.

Indication for capsule endoscopy	n = 54
Blood loss	
Recurrent iron deficiency anaemia	39
Recurrent GI bleeding	13
Possible neoplasm	
Further investigation following suspicious findings on another GI investigation	2
Further investigation following removal of GI neoplasms	2
Investigation of possible small bowel obstruction	1
Others	
Crohn's disease assessment	2
Chronic diarrhoea	2
Unspecified abdominal symptoms	2
Recurrent GI pain	1
Peutz-Jeghers syndrome review	1

¹ Note: several participants had more than one indication for capsule endoscopy

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Table 2. Association between hyperlipidaemia and diabetes status and other predictors and presence of small bowel xanthomas on capsule endoscopy.

Predictor status	Xanthomas of Total (%)	IRR ¹	95%CI	P-value ²
Predictor 1: Hyperlipidaemia status categories³				
No prior hyperlipidaemia and current TC<5.2mmol/L (comparator category)	5 of 17 (29.4%)	1.00		
No prior hyperlipidaemia and current TC≥5.2mmol/L	3 of 10 (30.0%)	1.40	(0.42 to 4.63)	0.59
Prior hyperlipidaemia not on anti-lipid medication	1 of 3 (33.3%)	2.29	(0.47 to 11.1)	0.30
Prior hyperlipidaemia on anti-lipid medication	11 of 24 (45.8%)	4.43	(1.32 to 14.9)	0.048
Predictor 2: Diabetes status categories				
No prior DM diagnosis (comparator category)	15 of 42 (35.7%)	1.00		
Prior DM diagnosis not on DM medication	3 of 5 (60.0%)	1.48	(0.55 to 3.95)	0.44
Prior DM diagnosis on DM medication	2 of 7 (28.6%)	0.52	(0.20 to 1.37)	0.37
Predictor 3: End-organ disease status				
No end-organ disease (comparator category)	17 of 45 (37.8%)	1.00		
End-organ disease present	3 of 9 (33.3%)	0.35	(0.14 to 0.86)	0.022
Predictor 4: Alcohol intake status				
Alcohol units per week ⁴	Mean 2.88 (SD 6.08)	1.91	(1.32 to 2.78)	0.0007

² Incidence rate ratio for the presence of xanthomas, estimated using multivariate Poisson regression (IRR; 95% confidence intervals; P-values); each predictor variable estimate is adjusted for the presence of the other three predictor variables.

³ P-values were corrected for multiple comparisons where appropriate using the Holm method.

⁴ Patients were classified according to their lipid status into four groups: 1) no current lipid abnormalities (TC<5.2mmol/L) and not on medications (N=17); 2) no past history of lipid abnormalities and not on medications, but current raised lipids (TC≥5.2mmol/L) (N=10); 3) past diagnosis of lipid abnormalities and not on medications, and current raised lipids (TC≥5.2mmol/L) (N=3); 4) past diagnosis of lipid abnormalities on lipid-lowering medication, whatever the current lipid levels (N=24).

⁵ Alcohol intake (showing mean (SD)) is analysed as a continuous standardised normal transformed variable [(variable value – mean)/standard deviation], with the IRR representing the linear slope of the association between likelihood of presence of xanthomas and the alcohol intake; the IRR can be thought of as the slope of the relationship.