Misleading Presentation of Colorectal Cancer in an Otherwise Healthy Patient

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Abstract:

Background: Colorectal cancer (CRC) represents the second most common malignancy and the fourth most common cause of cancer deaths. CRC can manifest early with bright red bleeding per rectum, tenesmus, and altered bowel habits. These symptoms are often attributed to benign lesions, including anal fissure. Our objective is to highlight the alarming scenario of an anal fissure masking the clinical features of an underlying colorectal cancer in healthy middle-aged patients.

Case Report

Our case report aims to discuss how congruent clinical features of benign-looking anal fissure can delay the diagnosis of rectal cancer. In January 2019, a healthy forty-four years old Iraqi male with no family history of colorectal neoplasms presented to Baghdad Medical City. He suffered from a long-standing peri-anal pain and infrequent bowel motion that was initially diagnosed as an anal fissure. Subsequent clinical assessment, with endoscopy, confirmed the presence of colorectal adenocarcinoma. We also carried out analytics, using Google Trends, to assess the spatiotemporal mapping of web users interested in case scenarios similar to our patient.

Conclusion

Anal fissure could coexist with colorectal cancer, even in younger patients. Therefore, it is essential to consider anal fissure and colorectal cancer on clinical assessment. Follow-up visits are paramount to exclude underlying life-threatening aetiology at secondary care.

Keywords: Colorectal cancer; Adenocarcinoma; Anal Fissure; Digital Epidemiology; Endoscopy; Fissure in Ano; Google Trends; Histopathology; Iraq; Predictive Epidemiology.

Introduction:

Colorectal cancer (CRC), also known as bowel cancer, colon cancer, or rectal cancer, is a cancerous growth affecting the colon, the rectum, or both [1]. The American Cancer Society estimates that around 1 in 21 men and 1 in 23 women in the United States will develop CRC during their lifetime [1, 2]. Worldwide, colorectal carcinoma is the second most common malignancy and the fourth most common cause of cancer death after lung, stomach and liver cancers [1]. In 2017, 52,331 new CRC cases were diagnosed in the UK, with an incidence rate of 41.7 per 100,000 person-year [2]. The incidence of colorectal carcinomas increases with age, and significantly beyond the age of fifty-

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five so that around 60% of cases affect patients 70 years or older [3]. Iraq has a low incidence of CRC but steady increment over time [3]. Both genetic and environmental factors play an essential role in the aetiology of colorectal cancer [4]. For instance, the most genetically-mediated CRC types include Lynch syndrome and Familial adenomatous polyposis, both are inherited in an autosomal dominant fashion [4]. Colon cancer typically affects older adults, though it can happen at any age, and it usually begins as small, noncancerous polyp inside of the colon that may transform over time to a cancerous growth [4]. Hence, many people with colon cancer experience no symptoms in the early stages of the disease, and when symptoms appear, they will likely vary, depending on the tumour size and location within the large intestine [4, 5]. Generally, physicians recommend people with an average risk of colon cancer to consider a colon cancer screening beyond the age of 50 years, while recommending people with an increased risk of CRC, such as those with a positive family history, to consider screening earlier [1, 2]. Researchers found

that some medications decrease the risk of precancerous polyps and CRC; for instance, some evidence points to aspirin and aspirin-like chemicals as protective agents [1-5].

Numerous lifestyle factors also influence the risk of developing colorectal cancer, including smoking, alcohol, body weight, and dietary patterns [4]. One-third of all colorectal carcinomas occur in the rectum with early symptoms, including bright red bleeding per rectum, tenesmus, and a change in bowel habit with more frequent and looser stool [1]. These symptoms are often attributed to benign causes in younger patients, so the diagnosis is usually delayed as with our patient. An anal fissure is an ulcer, or a tear, in the squamous epithelium of the distal anal canal [1,5]. It can occur in different locations, and the most common site is the posterior midline [5]. A fissure sited elsewhere around the anal circumference should raise the suspicion of a specific aetiology [1].

Objectives, Methods, and Ethics
Our study comprises a case report with a collateral statistical analysis of relevant data from Google Trends from 2004 to 2020. The primary objective is to bring readers' attention to potential coexistence of colorectal cancer in middle-aged patients presenting clinically as a case of a fissure-in-ano. Our case had novel findings in a patient with a cryptic colorectal cancer manifesting as an anal fissure in an otherwise healthy middle-aged Iraqi male. As a secondary objective, the Google search engine analytics will highlight potential deficit of knowledge of web users, including patients and physicians, on the possible association of colorectal cancer and anal fissure, by scrutinizing the spatial and temporal mapping of the surface web using specific search topics. The authors carried out the work described in this manuscript following the Code of Ethics of the World Medical Association [Declaration of Helsinki] on medical research involving human subjects, European Union (EU) Directive (210/63/EU), the uniform requirements for manuscripts submitted to biomedical journals, and the ethical principles defined in the Farmington Consensus of 1997.

Case Report and Discussion of the Literature
An otherwise healthy, non-smoker non-alcoholic forty-four years old Iraqi male with a negative past medical or family history suffered from a long history of peri-anal pain, presented to Baghdad Medical city in January of 2019. He presented with continuous peri-anal pain, radiating to the lower limbs that exacerbate by defecation. The onset of his pain was also associated with the infrequent passage of hard stools, once every four days. He was first seen by a surgeon at the outpatient clinic and diagnosed as a case of an acute posterior anal fissure at 6 o'clock position. He received conservative treatment consisting of stool softeners with a topical anaesthetic agent (lidocaine gel). Later, the surgeon scheduled a follow-up appointment two weeks later when the condition got worse with more severe pain. Accordingly, the doctor recommended conducting a surgical intervention, lateral sphincterotomy. However, the pain returned one week after discharging the patient from the hospital. Thus, he opted to self-medicate with various oral analgesics, including NSAIDs. Some months passed, and during August 2019, he presented to the accident and emergency department of Baghdad Teaching Hospital, after developing a sudden severe epigastric pain that progressed to a generalized abdominal pain with signs of peritonitis, including the presence of air under the diaphragm on erect abdominal X-ray.

Following a rapid hemodynamic stabilization, the patients underwent an emergency laparotomy which revealed a perforated duodenal ulcer. The defect was sutured successfully, and the one-week post-operative hospital stay was uneventful without any peri-anal pain, but again the same peri-anal pain recurred after a while from leaving the hospital, and at that time it was associated with bright red bloody stool with some blood clots. This time, the consultant surgeon, who reviewed the patient, decided to refer him for an urgent colonoscopy. Colonoscopy revealed a lower rectal circumferential mass, for which histopathology proved the diagnosis of invasive adenocarcinoma of the rectum (Figure 1). The physicians communicated the results to the patient, and they staged the disease using CT scans of the chest and the abdomen, by which they detected an irregular mass measuring 4*3*5 cm circumferentially infiltrating the rectum with multiple enlarged presacral and pararectal lymph nodes with no evidence of hepatic or pulmonary metastatic foci. Further, baseline tumour markers assay, chest X-ray, and abdominal ultrasound were also done. In January 2020, the patient was electively admitted to the surgical ward of Baghdad Teaching Hospital for abdominoperineal resection with a permanent end colostomy fashioning after being thoroughly assessed and counselled on the available treatment options by a multi-disciplinary team of surgeons and oncologists at the hospital.
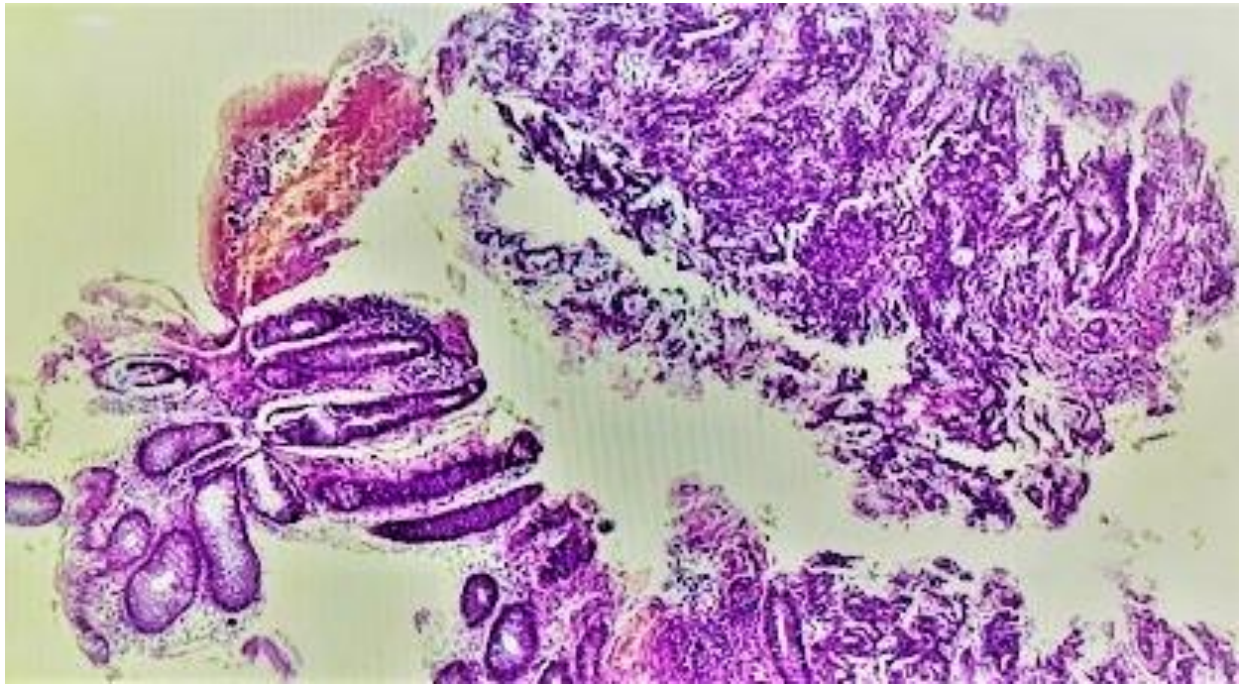
Figure 1: Histopathology of the tumour showing ulceration with infiltration by atypical epithelial cells arranged in an irregular villoglandular structure with desmoplastic stromal reaction.

Colorectal carcinoma in most populations has a lifetime risk of 3-5% [4]. According to the location and stage of the disease, the presentation may vary significantly from being asymptomatic, discovered by screening programs, or incidentally detected due to acute abdominal pain [7]. The most typical presentation is bleeding per rectum and change in bowel habits [7]. However, CRC located in the recto-sigmoid region usually presents with large bowel obstruction, while cancers in the ascending colon usually present with iron deficiency anaemia [7]. Individuals with an average risk, of an age between 50 and 75 should undergo CRC screening [8]. Recommendations for optimal surveillance intervals, preferred tests, and optimal timing when to start and stop screening differ regionally and should be considered for clinical decision-making [8]. Furthermore, the availability of local resources and patient preferences also influence CRC screening [8]. In developing countries, including Iraq, we believe there are still some people who do not follow standard screening guidelines for CRC, although a national CRC screening program is available at almost all tertiary healthcare centres. However, the lack of health education among those at risk, fear from invasive screening methods, the lack of awareness, and the limited access to such screening programs render those programs drastically less effective.

In relevance to the focus of this case report, a considerable number of studies were conducted, looking at the effectiveness of a spectrum of non-invasive screening tools as the guaiac and immunochemical faecal occult blood testing which is currently used in the early detection programmes for CRC, but none of these tools was proven to have a significant impact on all-cause mortality compared to using flexible sigmoidoscopy according to meta-

analysis results of all these studies combined. [9]. In our case report, the patient presented with signs and symptoms of anal fissure. Nonetheless, due to the persistence of clinical manifestations even following treatment, secondary causes of the peri-anal pain had to be suspected. Colonoscopy showed a suspicious lesion which was found to be an adenocarcinoma lying high within the wall of the rectum, which explains the negative findings on the digital rectal exam (DRE) on the two occasions when it was performed; the first time under general anaesthesia at the time of the surgical operation for his fissure, and the second at the colonoscopy unit.

Given the low prevalence of CRC in this young age group, meta-analyses showed that CT Colonography might be more suitable than optical colonoscopy for initial investigation of a suspected CRC as it has reasonable specificity, but that was not the case in our report due to the lack of such evidence in the local guidelines in place at the current time [10]. However, CT colonography and optical colonoscopy should be considered equivalent in CRC detection sensitivity and can also be deployed as a complementary tool [10]. Additionally, the pain character is a vital clinical feature to elicit a comprehensive and systematic history taking. A neuropathic type of pain with radiation to lower limbs, due to the involvement of sacral nerve roots, should trigger further suspicion, especially after the failure of some treatment modalities. Anal fissure and colorectal cancer can share similar risk factors which may complicate the clinical picture. For example, bad dietary habits such as a diet high in animal fat and low in fibres and chronic constipation are among the suspected risk factors of anal fissure [6]. Also, colorectal cancer is one of the causes of change in bowel habits and constipation which may predispose to fissure-in-ano

[1, 6]. We have endeavoured to compare the peculiar findings, and the other clinical data mentioned in this case report against the existing published evidence in literature in terms of similarities and differences between our case and other relevant case reports about the different presentations of colorectal cancer, especially rectal adenocarcinomas, but none was found presenting with anal fissure as in our case scenario. However, Barbeiro and coworkers (2016) reported in their case series that an early squamous cell carcinoma of the anus might be misdiagnosed in its early stage as an idiopathic anal fissure [11].

Google Trends Analytics: Worldwide and Iraq
We retrieved longitudinal data from Google Trends for the period from 01 January 2004 to 23 October 2020 by using two search topics "Colorectal cancer" and "Anal Fissure" [12]. Using Microsoft Excel 2016 and IBM SPSS version 24, we analyzed two datasets, one for the entire world and one for Iraq, to evaluate the spatial-temporal mapping of surface web users' interest in these two topics. In Iraq and concerning the geographic (spatial) mapping, two governorates were most interested in the topic "Anal fissure", Erbil and Baghdad (Figure 2). In comparison, nine governorates were most interested in the topic "Colorectal cancer", including Erbil, Duhok, Ninawa, Baghdad, Babil, Sulaymaniyah, Al-Najaf, Basrah, and Karbala (Figure 2). Iraqis were also interested in search topics with alternative keywords, including "اعراض سرطان القولون" and "سرطان القولون".
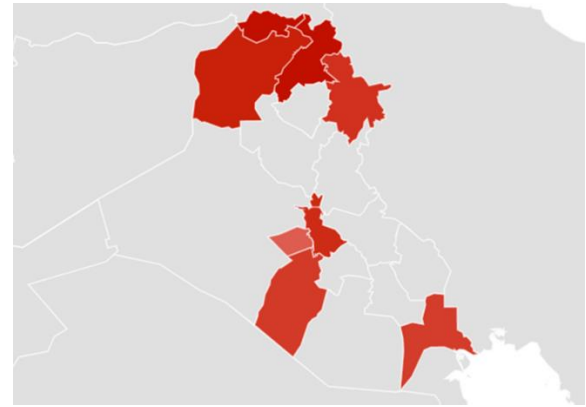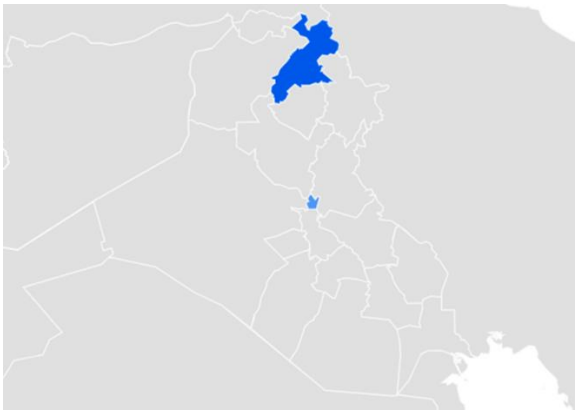

Figure 2: Spatial Mapping of Iraq: "Anal fissure" (left, blue colour-coding) and "Colorectal Cancer" (right, red colour-coding) Search Topics.

Worldwide and in connection with the spatial mapping, surface web users from sixty-five countries displayed the highest interest in the search topic "Anal fissure", the top twenty countries included Iran, Israel, Italy, Romania, Turkey, Greece, China, Canada, India, Brazil, the UAE, Algeria, Spain, Morocco, Pakistan, Japan, Australia, France, Ireland, and Germany (Figure 3). Countries from the Arab world and the Middle East also included Iran, Turkey, the UAE, Algeria, Morocco, Tunisia, Saudi Arabia, and Egypt. Concerning the search topic "Colorectal cancer", internet users of the highest interest were residents of sixty-eight nations, the top twenty of which included Taiwan, South Korea, Hong Kong, Paraguay, Spain, Jordan, Romania, Puerto Rico, New Zealand, United Kingdom, Norway, Panama, Philippines, Costa Rica, Australia, Lebanon, Algeria, Canada, Ireland, and Singapore (Figure 3). Web-users from the Arab world and the Middle East included Egypt, Saudi Arabia, Kuwait, the UAE, Morocco, Iraq, Iran, and Turkey.
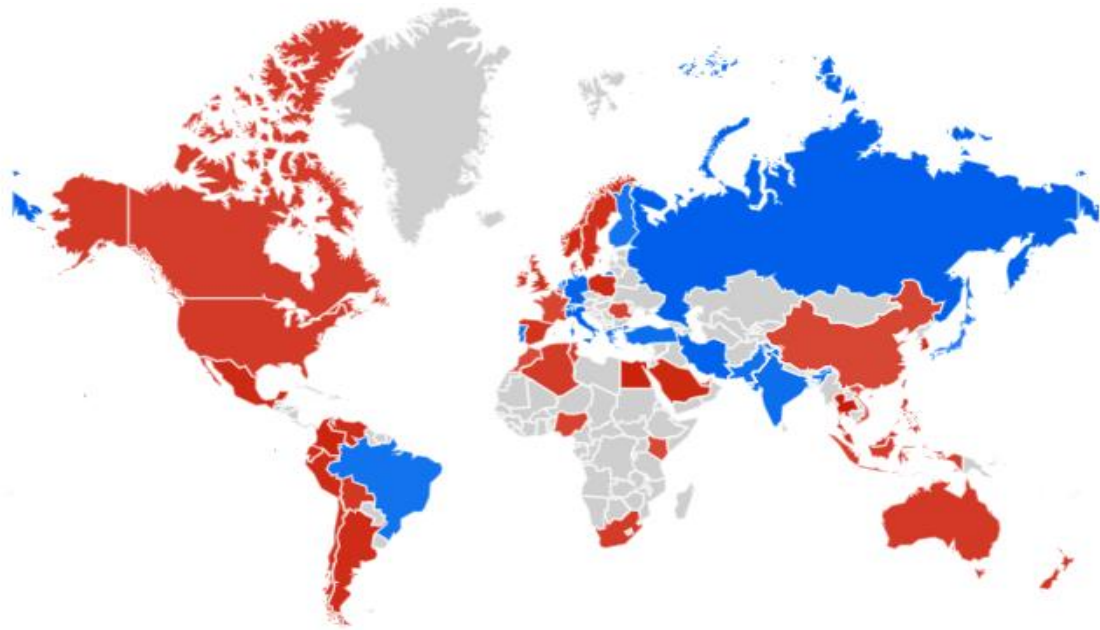
Figure 3: Spatial Mapping of the World: Colorectal Cancer (red) and Anal Fissure (blue).

In Iraq, temporal mapping (2004-2020) showed high variability with statistical outliers on March 2007, March and September 2007, March-April 2008, December 2009, and March-April as well as October 2010 (Figure 4). Worldwide, statistical outliers exhibited alternative timing as they appeared on January, April, August, and October 2004, and August-September 2020, and these were strictly related to the search topic "Colorectal cancer" (Figure 4). Accordingly, "Colorectal cancer" was the least predictable over time (Mean=46.50, Standard Error=0.477, R^2=0.3735, Coefficient of Correlation=0.7818, Polynomial Predictive Equation $y = 2E\text{-}11x^6 - 9E\text{-}09x^5 + 1E\text{-}06x^4 - 9E\text{-}05x^3 + 0.0039x^2 - 0.3171x + 58.514$) when compared to the search topic "Anal fissure" (Mean=35.04, Standard Error=0.393, R^2=0.847, Coefficient of Correlation=0.9349, Polynomial Predictive Equation $y = -9E\text{-}12x^6 + 6E\text{-}09x^5 - 2E\text{-}06x^4 + 0.0002x^3 - 0.012x^2 + 0.3451x + 26.218$). Nonetheless, each has a strong effect size.
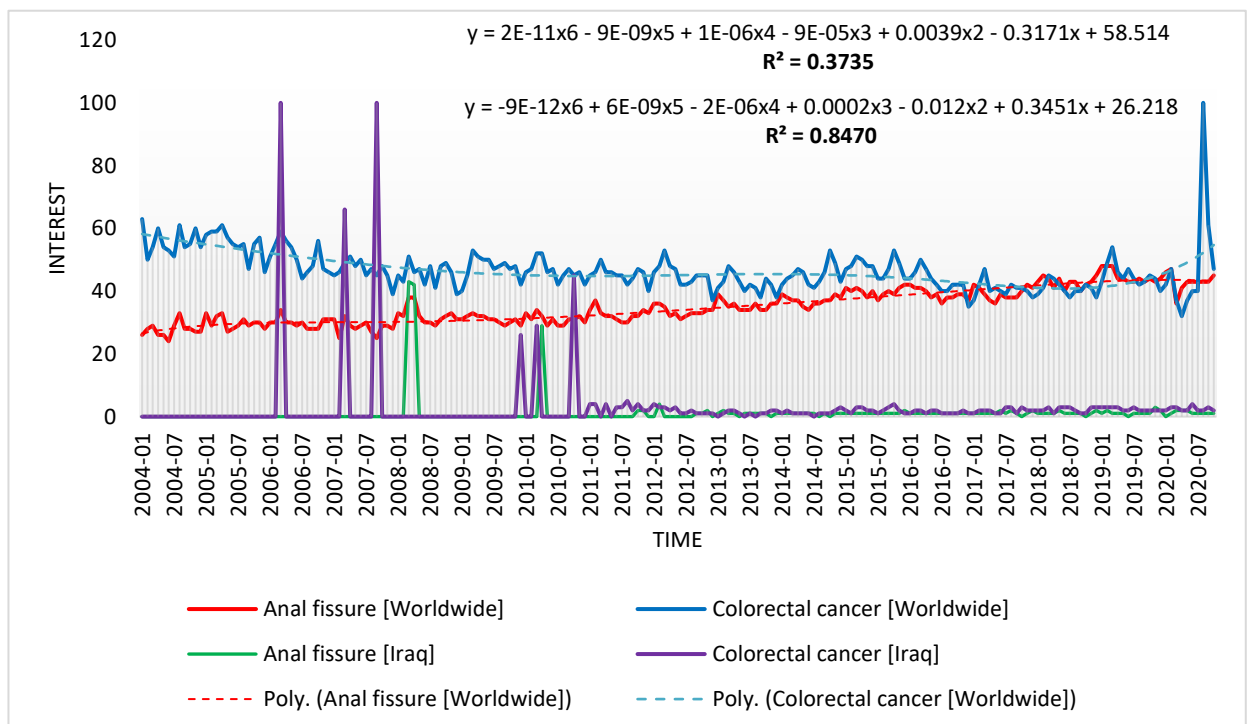

Figure 4: Temporal Mapping: Worldwide and Iraq .

When juxtaposing Iraq versus the world, Kendall's tau-b bivariate correlations confirmed significant correlation for "Anal fissure [Worldwide]" versus "Colorectal cancer [Worldwide]" (τb=-0.302, p-value<0.001), "Anal fissure [Worldwide]" versus "Anal fissure [Iraq]" (τb=0.605, p<0.001), "Anal fissure [Worldwide]" versus "Colorectal cancer [Iraq]" (τb=0.525, p<0.001), "Colorectal cancer [Worldwide]" versus "Anal fissure [Iraq]" (τb=-0.325, p<0.001), "Colorectal cancer [Worldwide]" versus "Colorectal cancer [Iraq]" (τb=-0.234, p<0.001), and "Anal fissure [Iraq]" versus

"Colorectal cancer [Iraq]" (τb=0.433, p<0.001). To summarize, significant bivariate correlations existed for all search terms, and these had a weak-to-moderate effect size (Table 1). Further, multivariate tests indicated a significant effect of the annual temporal variability, worldwide but not in Iraq, for the two search topics, "Anal fissure" (aR^2=0.880, df=16, Mean Square=348.647, F=93.174, p-value<0.001) and "Colorectal cancer" (aR^2=0.329, df=16, Mean Square=221.233, F=7.167, p<0.001).

Table 1: Bivariate Correlations: Kendall's tau-b (τb)

		Anal fissure [Worldwide]	Colorectal cancer [Worldwide]	Anal fissure [Iraq]	Colorectal cancer [Iraq]
Anal fissure [Worldwide]	τb Coefficient	1.000	-.302**	.605**	.525**
	Sig. (2-tailed)	.	.000	.000	.000
	N	202	202	202	202
Colorectal cancer [Worldwide]	τb Coefficient	-.302**	1.000	-.325**	-.243**
	Sig. (2-tailed)	.000	.	.000	.000
	N	202	202	202	202
Anal fissure [Iraq]	τb Coefficient	.605**	-.325**	1.000	.433**
	Sig. (2-tailed)	.000	.000	.	.000
	N	202	202	202	202
Colorectal cancer [Iraq]	τb Coefficient	.525**	-.243**	.433**	1.000
	Sig. (2-tailed)	.000	.000	.000	.
	N	202	202	202	202

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

In summary, the spatial mapping has a distinct geographic distribution for each of the two search topics, nationally in Iraq and worldwide. Similarly, the temporal mapping was also unique for each search topic, with different variances, the annual distribution of statistical outliers, predictability over the years, and bivariate correlations, nationally in Iraq and worldwide. Further, most of the bivariate correlations had no substantial effect size, unlike the multivariate tests. All these results gave us evidence that there is a heterogeneous distribution of surface web users who exhibited different interests in two distinct topics, "Colorectal cancer" and "Anal fissure", at a national level in Iraq as well as worldwide, which is in harmony with our case report on the lack of awareness of potential association of anal fissure and colorectal cancer, by patients as well as physicians.
Future studies should incorporate a cohort of patients with sufficient sample size and a male-to-female ratio representative of the underlying population. Researchers should attempt to study and compare different ethnicities and age groups. Overcoming the limitations of data analytics, machine learning algorithms, and the statistical package can also serve as leverage for reliable subsequent studies in line with the current study's methodology and objectives [13-15]. Investing in the application of artificial intelligence, including machine learning, is priceless, especially when it comes to analyzing big data by deploying real-time and predictive analytics [16-19]. Further, anticipated studies on the association of colorectal cancer and anal fissure can be either purely observational as cross-sectional analytics, retrospective studies, prospective cohorts or within

the context of the higher hierarchy quasi-experiments, randomized case-control trials, aggregate studies, and meta-analytic studies of the premium level-of-evidence [20].

Conclusions
An anal fissure can be a secondary complication to colorectal cancer even in younger age groups, less than forty-five years of age. It is crucial to consider anal fissure and colorectal cancer on clinical assessment to coexist. When the patient visits the surgeon as early as possible, colorectal adenocarcinoma can disguise itself as an apparent anal fissure. We opine that a delay in the diagnosis in our case scenario is due to an improper history taking, limitations to perform the digital rectal exam in patients with an anal fissure, failure to communicate the importance of follow-up visits to the patient, and the lack of risk factors in this particular patient, in which the fissure assumed its typical surgical position.

Conflict of Interest
The authors declare that they have no conflict of interest, and they have self-funded this study.

Availability of Data
Our Data, including raw dataset for Google Analytics, are available upon request from the corresponding author.

Authors' Contribution: Mustafa Aljarshawi, Haitham Albadree, and Hasan Bahar interviewed the case in our study, conducted the literature review, and

wrote the first draft of the manuscript. Ahmed Al-Imam collected the data from Google Trends, conducted data analytics, revised the first draft of the article, and prepared the manuscript for scholarly submission.

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عرض مضلل لسرطان القولون والمستقيم لدى مريض يتمتع بصحة جيدة

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