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DATABASE ANALYSIS

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Adult Intussusception in Jordan: Demographics, Clinical Features, and Outcomes from a Tertiary Hospital

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Background: Adult intussusception (AI) is a rare condition with diverse clinical presentations and management challenges. Despite its rarity, understanding its epidemiology, clinical features, and predictive factors distinguishing benign and malignant lead points is crucial for effective management. This study aimed to assess the demographic and clinical characteristics of patients with pathological AI and examine factors associated with malignant lead points.

Material/Methods: Medical records of patients aged >18 years with diagnosis of AI between January 1, 2014, and January 1, 2024 were retrospectively analyzed. Patients were classified based on location and etiology of intussusception. Predictive factors for malignant lead points were assessed, including age, sex, presenting symptoms, location, and size of intussusception. Computed tomography (CT) scan images were reviewed for diagnosis confirmation. Transient small bowel intussusceptions and intussusceptions related to feeding tubes were excluded.

Results: Twenty-six cases of pathological AI were identified over 10 years, with a male predominance (69.2%) and a mean age of 53.3 years. Abdominal pain was the most common presenting symptom (65.4%), with bowel obstruction diagnosed in 23.1% of cases. CT scans were the primary diagnostic modality (92.3%). Colocolic intussusceptions were most prevalent (53.8%), and surgical management was common (69.2%). Histopathological examination revealed benign lead points in the majority (57.7%) of cases, with lipomas and polyps being the most common. Bleeding per rectum was significantly associated with malignant lead points (P=0.011).

Conclusions: AI presents with diverse clinical features. It predominantly affects the colon. Bleeding per rectum indicates a higher likelihood of malignant lead points. A multidisciplinary approach is essential for optimal case-based management.

Keywords: Adult • Intussusception • Pathologic Processes • Pathological Conditions, Signs and Symptoms • Abdomen, Acute • Radiology

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Introduction

Intussusception is considered rare in adults, accounting for 1% to 5% of bowel obstruction cases, in contrast to its common occurrence in children [1,2]. A pathological lead point is identified in 70% to 90% of AI cases [1,2]. In clinical practice, 90% of AI cases are confined to either the small or large bowel, with most being of the entero-enteric type [2-4]. The remaining 10% involve intussusception in the stomach or a surgically made stoma [4].

The presenting symptoms of AI are nonspecific and might be acute, subacute, or long standing. Abdominal pain is one of the commonest presenting symptoms. A variety of other symptoms including abdominal mass, change in bowel habits, hypoactive to absent bowel sounds, fever, and bleeding could be encountered in practice [4]. The classical pediatric triad of intussusception of abdominal mass, colicky abdominal pain, and bloody stool is rarely found in adults [4]. Due to this wide variety of symptoms and clinical manifestations, preoperative diagnosis of AI remains challenging. The most sensitive diagnostic method for intussusception is computed tomography (CT). It has the advantage over other imaging techniques due to its ability of defining the location, nature, and relationship of a mass to the surrounding tissue, in addition to its role in staging suspected malignancies [2,4].

There is no universal approach for the optimal management of AI. Most researchers recommended the surgical approach through laparotomy or laparoscopy, followed by resection. There is controversy whether or not the reduction of the intussusception should be done intraoperatively [2-4]. Some reports support resection without reduction in case of malignancy, to decrease the risks of perforation and dissemination of malignant cells [2]. Other researchers support resection with reduction when the diagnosis of a benign lesion has been established or when the resection can result in short gut syndrome [4].

Many prior studies and extensive reports have thoroughly investigated the various aspects of AI, including its epidemiology, the radiological features among different modalities and intussusception subtypes, diverse treatment options, and predictive factors for surgical intervention [1-15]. However, only scarce reports have investigated the predictive factors that can distinguish between benign and malignant lead points [7,16]. Notably, despite the considerable body of literature on AI, and to the best of our knowledge, no previous reports have discussed this topic in the Middle East. Therefore, this study aimed to assess the demographic and clinical characteristics of patients with pathological AI and examine factors associated with malignant lead points.

Material and Methods

This retrospective cohort study was conducted on the Jordanian population at King Abdullah University Hospital, a tertiary care center affiliated with Jordan University of Science and Technology. The study adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, as recommended by the EQUATOR network. Institutional Review Board (IRB) approval was obtained, and written informed consent was waived due to the retrospective nature of the study, in accordance with the IRB regulations at Jordan University of Science and Technology.

Cases were identified using the Dedalus Enterprise Management Health Information System (Version 12.13.2, Dedalus Group, Florence, Italy), by searching for the keyword "intussusception". The inclusion criteria were patients aged >18 years with a discharge diagnosis of intussusception via surgical findings or CT between January 1, 2014, and January 1, 2024. The exclusion criteria were patients under the age of 18, those with transient intussusceptions, or intussusceptions related to feeding tubes. A standardized data collection form was used by a senior radiology resident to extract patients' demographics, clinical presentation, radiological findings, and management. CT scan images for the included patients were reviewed by a radiologist with 13 years of experience who was blinded to patients' final diagnosis and outcome to minimize bias. The size of intussusception was determined by referring to the archived images where the maximum anteroposterior and transverse diameters of the intussusception were measured on axial images using the electronic caliper on the Picture Archiving and Communication System (Fujifilm Medical Systems, Version 7.1, Lexington, MA, USA). In cases in which the archived CT scan was not available, the size was determined by referring to the archived radiological reports (3/26). However, these measurements were excluded from the calculation of the mean to avoid introducing bias into the results. Patients were classified according to the site of intussusception into 3 groups, including enteroenteric, ileocolic, and colocolic intussusceptions. Intussusception was further classified according to its etiology into idiopathic intussusception, intussusception with benign pathological lead points, and intussusception with malignant pathological lead points. The predictive factors associated with malignant lead points that were studied included age, sex, presenting symptoms, location of intussusception, and the size of intussusception at the time of diagnosis. These were selected based on previous literature, as well as our clinical experience.

Data were analyzed using IBM SPSS version 24. Percentages were used to describe categorical variables. The chi-square test was used to assess the association of the studied variables with the presence of malignant lead points. Independent *t* test was used to compare the mean anteroposterior diameter

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Table 1. Summary of patients' characteristics.

Case	Age (Y)	Sex	Vomiting	Abdominal pain	Bowel obstruction	Bleeding per rectum	Constipation	Stool incontinence	Size (AP, cm)
1	64	F	Yes	No	No	No	No	No	2.5
2	74	F	No	No	No	No	No	No	3.6
3	52	F	No	No	No	No	No	No	3.4
4	63	F	No	No	No	Yes	Yes	No	3.9
5	44	F	Yes	Yes	Yes	No	Yes	No	6.8
6	28	F	Yes	Yes	Yes	Yes	Yes	No	Per report
7	34	F	Yes	Yes	No	No	No	No	Per report
8	71	F	No	Yes	No	No	No	No	Per report
9	68	M	Yes	Yes	Yes	No	Yes	No	4.2
10	41	M	No	Yes	No	Yes	No	No	5.8
11	62	M	No	No	No	Yes	No	No	5.1
12	35	M	No	Yes	No	Yes	No	No	6.4
13	70	M	No	Yes	No	No	No	No	5
14	47	M	No	Yes	No	No	No	No	6.3
15	19	M	No	Yes	No	No	Yes	No	5.1
16	78	M	Yes	Yes	Yes	No	Yes	No	8.4
17	77	M	No	Yes	No	No	No	No	6.4
18	47	M	No	Yes	No	No	No	No	7.8
19	39	M	Yes	Yes	Yes	No	Yes	No	6.6
20	21	M	No	No	No	No	No	No	3.4
21	30	M	No	Yes	No	No	Yes	No	7
22	72	M	No	No	No	No	No	No	3.5
23	61	M	No	Yes	No	No	No	No	5.3
24	57	M	No	No	No	Yes	No	Yes	7.1
25	57	M	Yes	Yes	Yes	No	Yes	No	No images per surgical findings
26	74	M	No	No	No	Yes	No	No	No images per endoscopy

Case	Size (T, cm)	Benign vs malignant	Location	Treatment	Pathological diagnosis
1	7.3	Benign	SBI (duodenal)	Surgical	Polyp (tubular adenoma with low grade dysplasia)
2	4.4	Benign	Ileocolic	Conservative	Lipoma
3	4.5	Benign	Colocolic	Surgical	Polyp (rectal and cecal hyperplastic polyps with no dysplasia or malignant features)
4	3.6	Malignant	Colocolic	Surgical	CRC

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Table 1 continued. Summary of patients' characteristics.

Case	Size (T, cm)	Benign vs malignant	Location	Treatment	Pathological diagnosis
5	6.2	Benign	Colocolic	Surgical	Lipoma
6		Malignant	Colocolic	Surgical	CRC
7		Benign	Ileocolic	Surgical	Polyp (inflammatory fibroid polyp)
8		Malignant	Ileocolic	Surgical	CRC
9	4.8	Malignant	Colocolic	Surgical	CRC
10	5.8	Malignant	Colocolic	Palliative care	CRC
11	6.5	Malignant	Colocolic	Surgical	CRC
12	5.4	Malignant	Colocolic	Unknown*	CRC
13	6.9	Benign	Ileocolic	Surgical	Appendicitis
14	4.6	Malignant	Colocolic	Palliative care	CRC
15	12.1	Benign	Ileocolic	Surgical	Lipoma+ appendicitis
16	5.5	Benign	Ileocolic	Surgical	Lipoma
17	6.2	Malignant	SBI (jejunal)	Surgical	Invasive adenocarcinoma of jejunum
18	8.1	Benign	Colocolic	Conservative	Lipoma
19	11.5	Benign	SBI (ileal)	Surgical	Crohn's
20	3.4	Benign	SBI (jejunoileal)	Conservative	Polyp (Peutz-Jegher's syndrome)
21	4.6	Malignant	Colocolic	Surgical	CRC
22	3.3	Benign	Colocolic	Conservative	Diverticulitis
23	4.7	Benign	Ileocolic	Conservative	Appendiceal mucocele
24	6	Malignant	Colocolic	Surgical	CRC
25		Benign	SBI (ileal)	Surgical	Submucosal fibrous nodule of small intestine
26		Benign	Colocolic	Surgical	Polyp (tubulovillous adenoma with high grade dysplasia)

M – male; F – female; AP – anteroposterior; T – transverse; SBI – small bowel intussusception; CRC – colorectal cancer. * Completed treatment outside.

and mean transverse diameter between patients with intussusceptions associated with benign lead points and patients with intussusceptions associated with malignant lead points. Multivariate analysis was not conducted due to small sample size. A *P* value of <0.05 was considered significant. No formal sample size calculation or power analysis was conducted because the study was retrospective in nature and included all available cases of AI within the specified time frame.

Results

Over the course of the 10-year study period, 26 cases of pathological AI were identified (**Table 1**). Male patients predominated the cohort, constituting 69.2% (n=18). The mean age of patients was 53.3 years (SD 18.1). Most patients (n=12, 46.2%) were above 60 years of age. Abdominal pain was the most common presenting symptom, which was documented in 17 (65.4%) patients. **Table 2** shows the demographic and clinical characteristics of patients. Bowel obstruction was diagnosed in 6 (23.1%) patients.

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Table 2. The sociodemographic and clinical characteristics of 26 Jordanian patients with diagnosis of adult intussusception.

Demographics	Number of patients n (%)
Age (years)	
19-40	7 (26.9%)
41-60	7 (26.9%)
>60	12 (46.2%)
Sex	
Male	18 (69.2%)
Female	8 (30.8%)
Presenting symptoms*	
Abdominal pain	17 (65.4%)
Vomiting	8 (30.8%)
Bleeding per rectum	7 (26.9%)
Constipation	9 (34.6%)
Stool incontinence	1 (3.8%)
Bowel obstruction	6 (23.1%)
Location	
Colocolic	14 (53.8%)
Ileocolic	7 (26.9%)
Small bowel	5 (19.2%)

Demographics	Number of patients n (%)
Etiology	
Idiopathic	0 (0%)
Bening lead point	15 (57.7%)
Malignant lead point	11 (42.3%)
Size (mean)	
Anteroposterior diameter of benign lead points	5.1 cm (SD=1.9)
Transverse diameter of benign lead points	6.5 cm (SD=2.9)
Anteroposterior diameter of malignant lead points	5.8 cm (SD=1.16)
Transverse diameter of malignant lead points	5.3 cm (SD=0.9)
Treatment	
Surgical	18 (69.2%)
Palliative	2 (7.7%)
Conservative	5 (19.2%)
Not known	1 (3.8%)

* Please note that many patients presented with more than 1 symptom. SD – standard deviation.

In most patients, 92.3% (n=24), the diagnosis was made preoperatively by means of CT. In 1 patient the diagnosis was made endoscopically and confirmed surgically. In another patient, the diagnosis was made intraoperatively, with no preoperative images available at our institution. Most of the intussusceptions were of the colocolic type, representing 53.8% (n=14) of cases. Small bowel pathological intussusceptions were the least common, representing 19.2% (n=5) of cases, in which 2 were seen in the ileum, 1 was jejunoileal, 1 was jejunal, and 1 was duodenal (**Figure 1**). Most of the intussusceptions were managed surgically 69.2% (18/26), while 2 patients received palliative care, due to metastatic colon cancer at the time of presentation. One patient completed his treatment at an outside institution, and 5 patients were treated conservatively.

The histopathological cause of intussusception was identified in all patients who were treated surgically, while in patients who were treated conservatively the diagnosis was based on CT scan (**Table 3**). Benign lead points were the most common, representing about 57.7% (15/26) of cases. Lipomas (**Figure 2**) and different types of polyps were the most common pathological benign lead points, constituting 33.3% each (5/15). One of these patients aged 19 years (the youngest patient in the cohort) had 2 pathological lead points, which were lipoma concomitant with acute appendicitis, and the intussusception was of the ileocolic type. This patient was treated with right hemicolectomy, and the diagnosis was confirmed by histopathology. In another patient, with ileocolic intussusception secondary to an inflammatory fibroid polyp, the patient had a prior presentation, with a transient jejunal intussusception 1 year before. As for the malignant pathological lead points, they were mostly located in the colon (90.9%, 10/11), and colon cancer was the most common histopathological diagnosis (**Figure 3**). There was 1 case of invasive adenocarcinoma seen in the jejunum, where the patient presented with jejunojejunal intussusception and small bowel obstruction (**Figure 4**).

Table 4 shows the distribution of benign and malignant lead points according to different variables. The mean anteroposterior diameter for intussusceptions associated with benign lead points was 5.1 cm (SD=1.9), compared with 5.8 cm (SD=1.16) in intussusceptions associated with malignant lead points (*P*=0.358). The mean transverse diameter for intussusception associated with benign lead points was 6.5 cm (SD=2.9), compared with 5.3 cm (SD=0.9) for malignant lead points (*P*=0.244). Bleeding per rectum was significantly more common in intussusceptions associated with malignant lead points, compared with intussusceptions associated with benign lead points (54.5% vs 6.7%, *P*=0.011).

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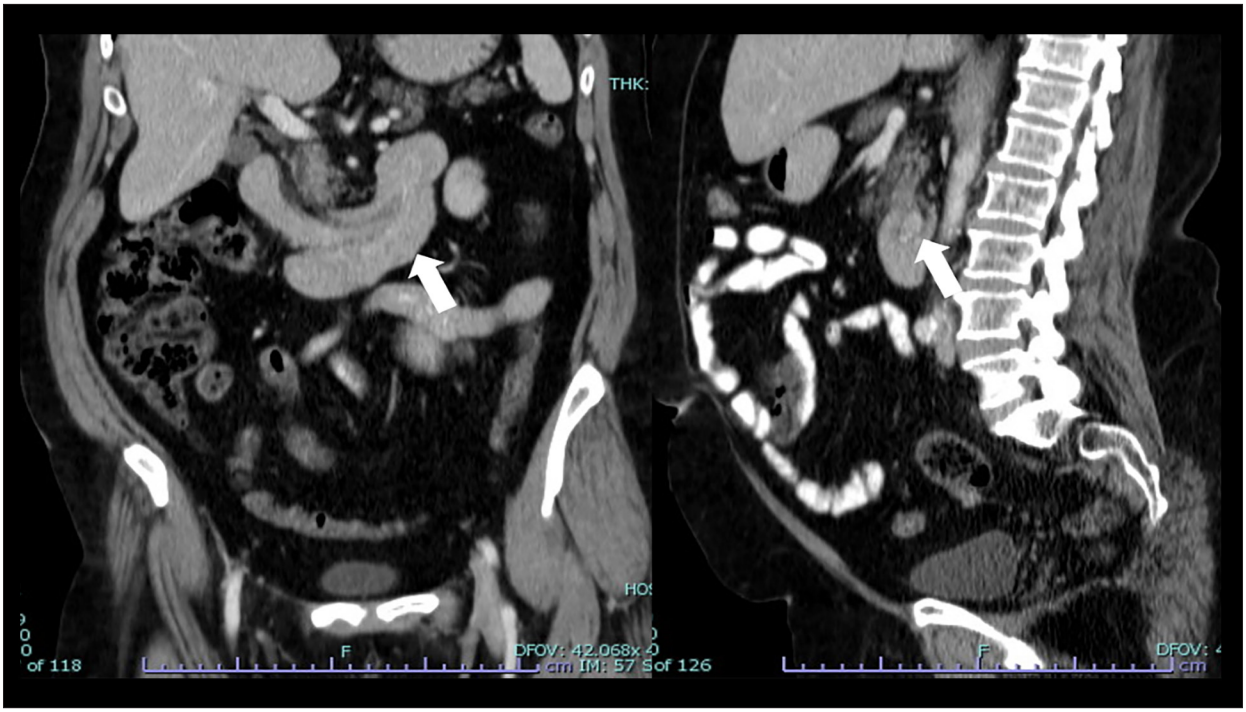

Figure 1. Coronal CT scan reconstruction with oral and intravenous contrast for a 64-year-old woman, demonstrating a segment of duodenal intussusception (arrow). Sagittal CT scan reconstruction for the same patient, demonstrating an enhancing polypoidal lesion (arrow) as a lead point for the lesion. The patient underwent surgical resection, which showed a tubular adenoma with low grade dysplasia.

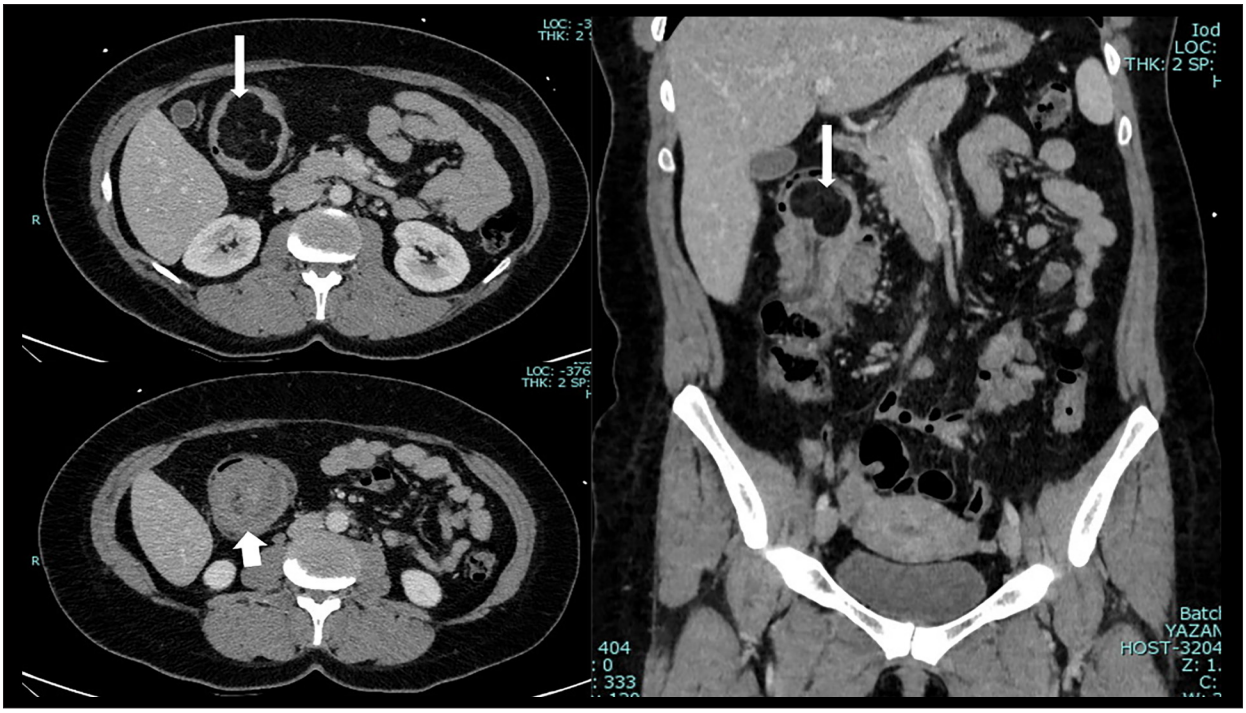

Figure 2. Axial CT scan at 2 different levels with oral and intraveous contrast for a 44-year-old woman showed a fat density lesion seen at the hepatic flexure (thin arrow) causing colocolic intussusception (thick arrow). Coronal CT image for the same patient showing the fat density lesion with colocolic intussusception. The patient underwent right hemicolectomy, with a histopathological diagnosis of sub-serosal lipoma.

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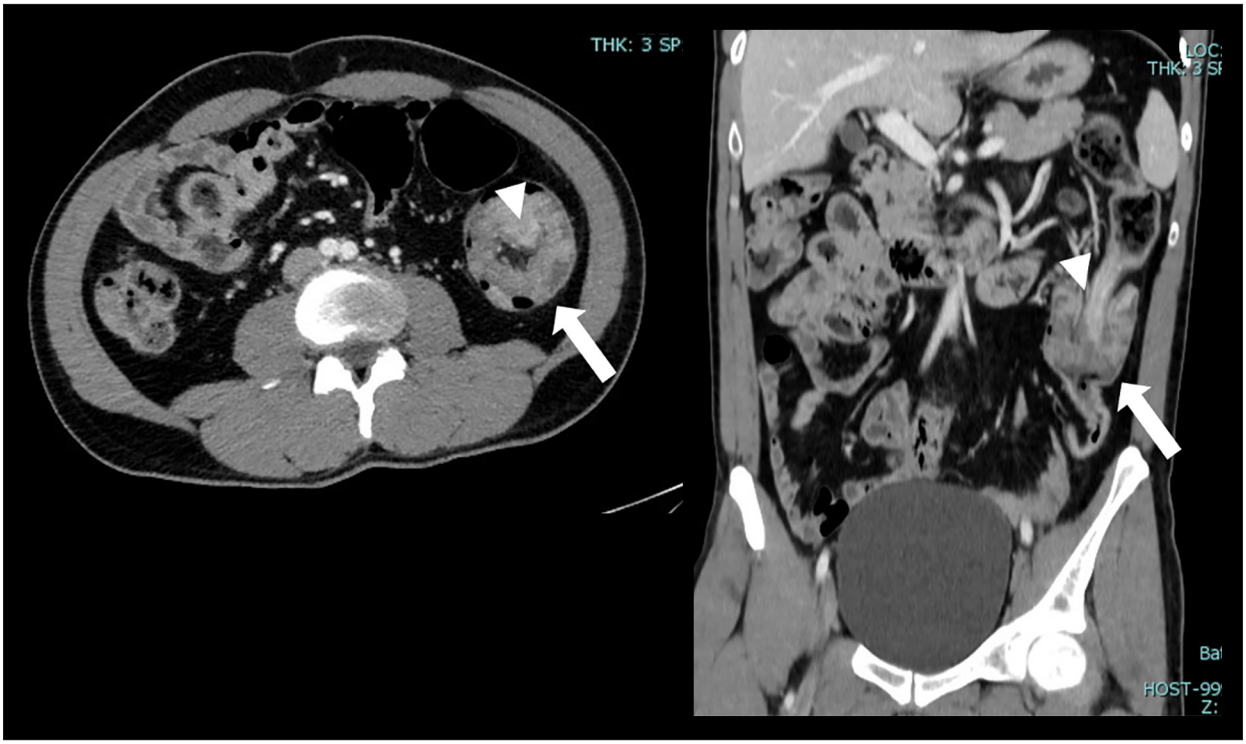

Figure 3. Axial and coronal CT scan with intravenous contrast for a 35-year-old man, demonstrating colocolic intussusception (arrows) just distal to the splenic flexure, with a circumferential wall thickening and a polypoidal mass (arrow heads). The patient had a confirmed diagnosis of colonic adenocarcinoma.

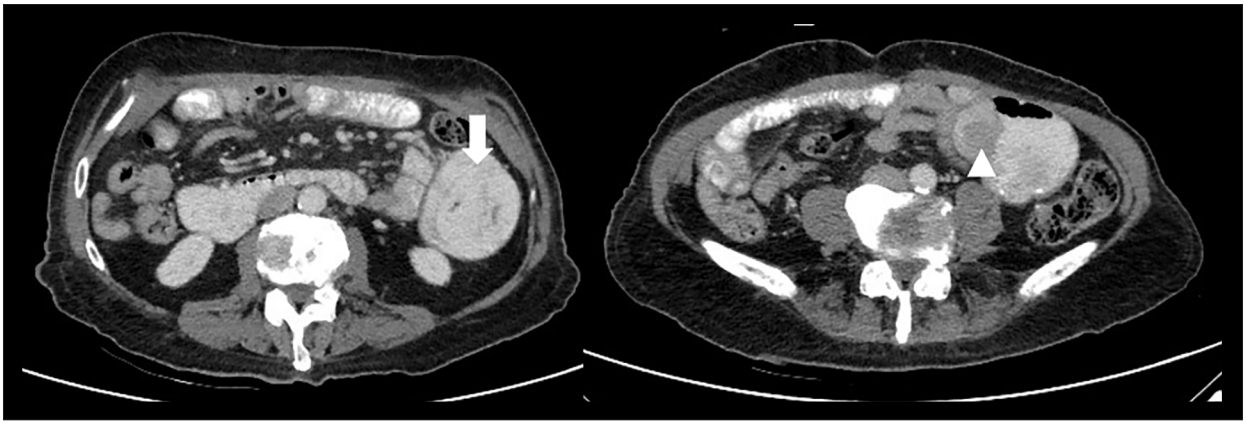

Figure 4. Axial CT scan with oral and intravenous contrast for a 77-year-old man at 2 different levels demonstrating jejunal intussusception (thick arrow) and a polypoidal mass (arrow head) acting as a lead point. The patient underwent surgical resection, with a histopathological diagnosis of small bowel adenocarcinoma.

Discussion

This study assessed the demographic and clinical characteristics of pathological AIs, reinforcing previous literature in the field. The incidence of pathological AI is rare. In this cohort, only 26 cases were found in the 10-year study period. The meta-analysis of Hong et al documented 1229 cases of AI in a 36-year search period [12]. The male predominance seen in our cohort aligns with what was reported in several previous studies [5,13,16,17]. However, in some other studies, female patients predominate the cohort [8,9,11]. This observation could suggest a potential population related sex susceptibility to the pathological lead points associated with AI, warranting further studies in a larger scale.

The mean age of 53.3 years in our study was concordant with the age range previously reported, of 50.5 to 57 years [7,14,15]. Furthermore, most patients in our cohort were above the age

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Table 3. Distribution and etiology of the different lead points.

Lead point*	No. of patients (%)
Malignant neoplasm	
Colon cancer	10 (38.5%)
Small bowel adenocarcinoma	1 (3.85%)
Benign neoplasm	
Lipoma	4 (15.4%)
Polyp	5 (19.2%)
Others	
Acute appendicitis	1 (3.85%)
Acute appendicitis + lipoma	1 (3.85%)
Acute diverticulitis	1 (3.85%)
Crohn's disease	1 (3.85%)
Mucocele	1 (3.85%)
Submucosal fibrous nodule of the small intestine	1 (3.85%)

* Please note that 1 patient had 2 concurrent lead points (lipoma and acute appendicitis).

of 60 years. Onkendi et al reported that 45% of patients in his cohort were above 50 years [15], supporting a similar trend of increasing number of cases of AI in older age group. As demonstrated in **Table 3**, there was almost equal distribution of benign vs malignant pathological lead points according to age group (P=0.998). However, this association was not evaluated thoroughly in the literature and cannot be fully ascertained in this small sized cohort, necessitating further studies in this regard.

Abdominal pain was the most common presenting symptom, which is consistent with what was previously reported [1,2,7-10,15,18]. However, there was diversity in the presenting symptoms of pathological AI, necessitating a high index of suspicion for accurate diagnosis and timely management.

A substantial proportion of our patients presented with acute bowel obstruction (23.1%). There was a wide variation in the reported incidence of bowel obstruction associated with AI in the literature. Duc et al reported bowel obstruction in 81.3% of 96 cases of AI [13], contradicting Tresoldi et al, who reported bowel obstruction in only 10% in a comparable cohort size of 93 cases [5]. In most other studies, the proportion of bowel obstruction ranged between 35% and 50% of cases [8,9,16]. Despite this variation, bowel obstruction remains an important well-known complication associated with AI that needs to be promptly diagnosed and managed to reduce the risk of bowel ischemia, perforation, or other morbidities.

Our study emphasizes the important role of CT in the preoperative diagnosis of pathological AI. Hong et al, in their meta-analysis, reported a pooled accuracy of CT scan in diagnosing AI of about 77.8% [12]. The increment in the preoperative diagnosis of AI underscores the importance of advanced imaging modalities in guiding clinical decision-making and surgical planning. Given the challenges of diagnosing AI clinically, CT can also provide valuable insights into the broad differential diagnosis of AI, which includes other causes of bowel obstruction, such as adhesions, inflammatory bowel disease, and various tumors.

AI can be classified according to its location. Colocolic intussusceptions have emerged as the most prevalent type of AI in our cohort. This is opposed to most previous studies, in which enteric intussusception was the most common location [4,5,8,9,15-17]. The location of enteric intussusception in the duodenum is rarely reported in the literature [14], with 1 case seen in our cohort (**Figure 3**). The differences in the location among different studies might be explained by the different population studied. In addition, the diversity in the location of AI among previous studies highlights the need for a comprehensive evaluation and tailored management plans based on the anatomical location of intussusception and the type of lead point.

Histopathological examination of surgical specimens provided crucial insights into the underlying etiology of intussusception in our cohort. Benign lead points, including lipomas and polyps, were identified as the predominant type in our cohort, consistent with prior reports [6-8,16]. Many series in the literature found that most of the colonic lead points were malignant [1,6,7,9,16]. This is in concordance with our study, in which 72.7% of the lead points in colocolic intussusceptions were caused by colorectal cancer. Notably, our study identified bleeding per rectum among the different studied variables (**Table 4**), as a significant clinical feature associated with malignant lead points, emphasizing the importance of thorough clinical evaluation and consideration of malignant etiologies in high-risk patients. Few studies in the literature have investigated the predictive factors associated with malignant lead points in AI. Kim et al, in their cohort, demonstrated that chronic symptoms and colonic location of AI are associated with malignant lead points [7]. In another larger study, the age of the patient, presence of anemia, and location of the intussusception were predictive factors of malignant lead points [16]. However, in the same study [16], rectal bleeding as a symptom was not a predictive factor of malignancy, contradicting our results. These studies, like ours, were based on small cohorts, warranting further studies in a larger scale and from different

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Table 4. The distribution of benign and malignant lead points among different variables.

Variable	Benign		Malignant		*P* value*
	n	%	n	%	
Age					
19-40 years	4	26.7	3	27.3	0.998
41-60 years	4	26.7	3	27.3	0.998
>60 years	7	46.7	5	45.5	0.957
Sex					
Female	5	33.3	3	27.3	0.543
Male	10	66.7	8	72.7	0.543
Symptom					
Vomiting	6	40.0	2	18.2	0.228
Abdominal pain	9	60.0	8	72.7	0.402
Bowel obstruction	4	26.7	2	18.2	0.491
Bleeding per rectum	1	6.7	6	54.5	0.011
Constipation	5	33.3	4	36.4	0.598
Stool incontinence	0	0.0	1	9.1	0.423
Treatment					
Conservative treatment	5	33.3	0	0.0	0.051
Surgical treatment	10	66.7	8	72.7	0.051
Type					
Colocolic	5	33.3	8	72.7	0.137
Ileocolic	6	40.0	2	18.2	0.137
Enteric	4	26.7	1	9.1	0.137
Size					
Anteroposterior diameter	12	5.1 (1.9)**	9	5.8 (1.16)**	0.358
Transverse diameter	12	6.5 (2.9)**	9	5.3 (0.9)**	0.244

* $P<0.05$ is considered clinically significant. ** Represents the average diameter in cm, with standard deviation (not percent) in parentheses ().

populations, to find the exact clinical, imaging, and laboratory predictive factors of malignant lead points in AI.

Among our studied cohort, there was a case of submucosal collagenous fibroma in a 34-year-old woman. Interestingly, this patient had 2 episodes of intussusception 1 year apart. The first episode was transient jejunal intussusception, not related to the site of the lead point. This can support the theory that alteration of bowel motility has a role in the pathogenesis of intussusception [18]. No cases of idiopathic intussusception were seen in our study. This can be explained by the small sample size and the higher incidence of colocolic intussusception in our study, which was mostly associated with malignant lead points. There was a case of intussusception caused by cecal lipoma with concomitant acute appendicitis. Only 2 cases of similar coincidence were reported in the literature. One case was of a 56-year-old woman who presented with ileoileal intussusception secondary to lipoma concomitant, with acute appendicitis [19]. The other case was of a 43-year-old man who presented with colocolic intussusception secondary to lipoma and acute appendicitis [20].

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Surgical intervention remained the cornerstone of management for most patients in our study, regardless of whether the lead points were benign or malignant (**Table 4**). This reflects the consensus in the literature regarding the surgical treatment of intussusception associated with lead points [5,15]. The ultimate goal of prompt surgical intervention in these cases is to prevent complications and achieve favorable outcomes. However, the identification of benign and malignant lead points underscores the heterogeneity in etiological factors contributing to AI, necessitating a multidisciplinary approach to optimize patient care.

Although our study provides valuable insights into the clinical characteristics and management of AI, it is important to acknowledge certain limitations. First, the retrospective design may have introduced selection bias. Second, the relatively small sample size limits the statistical power of our findings. Additionally, since this study was conducted at a single center in Jordan, its generalizability to other populations can be limited.

Further prospective studies with larger, multicenter cohorts are warranted, to validate our findings and elucidate the predictive factors of malignant lead points that might affect the therapeutic strategies for this rare but clinically significant condition.

Conclusions

AI is a rare entity that is more common in men and was located mostly in the colon in our cohort. There is diversity in the presenting symptoms of AI, with abdominal pain being the most common one necessitating a high index of clinical suspicion. Bleeding per rectum is a significant clinical feature associated with malignant lead points. The heterogeneity of benign vs malignant lead points underscores the multidisciplinary approach for preoperative diagnosis and management planning of AI.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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