



Intussusception in children: lessons learned from intestinal lymphoma as a rare lead-point

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Abstract

Background Most cases of intussusception in children are idiopathic. Rarely, a malignant disease such as intestinal lymphoma may cause intussusception. Due to dramatic changes of expected outcome with chemotherapy regime alone, the surgical management of patients with intestinal lymphoma presenting with intussusception has to be reevaluated.

Methods Retrospective chart review from May 2011 to February 2017. We included all patients with intestinal lymphoma presenting with intussusception.

Results We found five patients with a mean age of 6.4 years (range 3–16). The most common presenting symptom was abdominal pain for several weeks which had acutely worsened. In all but one patient an ultrasound before pneumatic or hydrostatic reduction showed a finding suspicious of a pathological lead-point. Pneumatic or hydrostatic reduction was attempted in all patients, no complications were noted. In one patient reduction was not successful. Recurrence after reduction occurred in two patients. Two patients needed surgery, three had a percutaneous ultrasound-guided biopsy for diagnostic purposes. All patients had aggressive mature B cell non-Hodgkin lymphoma.

Conclusion A high index of suspicion for the presence of a pathological lead-point in children older than 4 years and children with recurrent intussusception is necessary in patients presenting with intussusception. Malignant, highly aggressive B cell non-Hodgkin lymphoma, although rare, must actively be searched for. Pneumatic or hydrostatic reduction should remain the first line treatment in most cases.

Keywords Intussusception · Lymphoma · Intestinal · Pneumatic reduction · Hydrostatic reduction

Background

Intussusception is a common pediatric surgical entity encountered in infants and young children with a peak between 3 and 12 months of age [1]. In most cases, the intussusception is idiopathic, however, in around 6% of cases a pathological lead-point (PLP) is found [2]. The older the child, the more likely it is to find a PLP [1, 2]. The most common lead-point is a Meckel diverticulum and it can lead to intussusception at any age [2]. Other PLP's are duplication cysts, juvenile polyps, intestinal submucosal

hemorrhage, and edema in patients with Schönlein-Henoch Purpura [1–5].

Most lead-points are benign, however, in rare cases, highly malignant mature B cell non-Hodgkin lymphoma (B-NHL) of the bowel wall may lead to intussusception [3]. Burkitt's lymphoma is the most common intestinal subtype of B-NHL⁶. In children, the most common site for intestinal lymphoma is the ileo-cecal region [6, 7].

We present a case series of five patients with intussusception triggered by intestinal lymphoma and the lessons we learned from treating these patients.

Methods

A retrospective search of our oncological database identified all children admitted to our hospital between May 1st 2011 and February 28th 2017 presenting with intussusception due to an intestinal lymphoma.

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A chart review of those patients was performed. Demographic variables, presenting symptoms, imaging, radiological intervention, outcome, as well as therapy and follow-up data were extracted for each patient.

Our local ethics committee approved this retrospective data analysis (BASEC-No 2018-01027).

Results

Between May 2011 and February 2017 five patients were admitted with ileo-cecal and/or ileo-ileal intussusception due to intestinal lymphoma. Three patients (60%) were male. At the time of diagnosis, median age of all patients was 6.4 years (range 3–16). The most common presenting symptom was abdominal pain ($n=5$), mainly abdominal spasms ($n=3$) for several weeks, which had acutely worsened. Weight loss ($n=3$), as well as nausea or vomiting ($n=3$) were also common. The classic clinical signs for intussusception—a palpable abdominal mass and bloody stools—were found in only one patient. One patient mentioned night sweats, one patient suffered from fever. One patient also complained of intermittent severe pain in both legs. Later she was found to be the only patient with stage IV disease with the involvement of the bone marrow (Table 1).

All patients had an initial abdominal ultrasound, which showed the presence of an ileo-colic intussusception. In four patients an irregularity or thickening of the bowel wall was noted which led to further diagnostic efforts to rule out a PLP. One of those four patients showed multiple hepatic lesions as well. No PLP could be detected in one patient on initial abdominal ultrasound.

The initial therapy in all patients was a pneumatic or hydrostatic reduction.

Patient 1 experienced recurrent intussusception after initially successful pneumatic reduction. A second reduction was not successful, follow-up ultrasound lead to the suspicion of Meckel diverticulum in the intussusceptum (Fig. 1). Explorative laparotomy with manual reduction revealed a discoid tumor of 2 × 2 cm diameter 60 cm proximal of the ileo-cecal valve as lead-point (Fig. 2). It was excised in toto by ileal segment resection.

Patient 2 also suffered from recurrent ileocolic intussusception after initially successful pneumatic reduction. An abdominal ultrasound and CT scan showed irregular excentric thickening of the bowel wall and good perfusion of the intussusceptum, as well as enlarged mesenteric lymphnodes. The second pneumatic and hydrostatic reduction attempt was only partially successful. Due to good perfusion of the intussusceptum, no signs of bowel obstruction and a pain-free patient, further reduction attempts were not undertaken. Ultrasound-guided percutaneous biopsies of the irregular bowel wall were taken.

In patient 3 the initial reduction was not successful and the patient was taken to the operating room for explorative laparotomy and manual reduction. Intraoperatively, a double intussusception (ileo-ileal into ileo-cecal) was found and the irreducible ileo-ileal intussusception containing the tumor had to be resected by ileal segment resection.

In patient 4 ultrasound revealed an ileo-cecal intussusceptum, and a thickened ileal bowel wall suspicious of lymphoma. Hydrostatic reduction was only partially successful. Yet as the patient was pain-free and a good perfusion of the intussusceptum was shown by Doppler ultrasound, it was decided to defer from repeated reduction attempts. MRI confirmed a tumor of the right lower abdomen and showed multiple nodular liver lesions. Ultrasound-guided percutaneous biopsies of the ileo-cecal tumor were taken.

In patient 5, the initial ultrasound at another hospital showed an ileo-colic intussusception. Repeat ultrasound at our institution showed a thickened ileum in a way that persistent intussusception could not be excluded. In this case, pneumatic reduction was performed and showed free passage of air into the distal ileum. It remains unclear, if the initial ultrasound showed the lymphoma or if there had been intussusception with spontaneous reduction by the time the reduction was performed. Abdominal MRI was performed which showed a tumor of the distal ileum likely to be lymphoma. An ultrasound-guided percutaneous biopsy was taken.

Histopathological work-up lead to the diagnosis of aggressive mature B-Non-Hodgkin lymphoma (B-NHL) in all five patients: four patients had Burkitt's lymphoma, one patient diffuse large B-cell lymphoma (DLBCL).

According to St. Judes staging system, stage I/II was found in two patients, stage III in two patients, and stage IV in one patient with bone marrow involvement, corresponding to the diagnosis of Burkitt's leukemia (B-AL) [8]. The post-operative or post interventional course was unproblematic in all but one, who suffered from an early postoperative small bowel obstruction and who had to undergo a relaparotomy with adhesiolysis. All patients were treated with chemotherapy according to the study protocols of the Berlin–Frankfurt–Münster group (BFM-NHL 04/12/13) [9, 10]. None of the patients experienced relapse of the disease with a mean follow-up time of 4.3 years (range 1.5–7 years).

Discussion

Malignant mature B cell non-Hodgkin lymphoma (B-NHL) as presented here is a rare PLP among patients with intussusception and offers a chance to learn some valuable lessons.

Even though B-NHL is a rare cause of intussusception up to 25% of patients with intra-abdominal B-NHL initially present with intussusception [11–13]. In pediatric patients,

Table 1 Patient characteristics

Patient No	Age (years), sex	Presenting symptoms	PLP diagnosis	Surgical therapy	Biopsy/resection	Histology/tumor size/staging	Stage (St. Jude)	Chemotherapy/risk group	Follow-up (years)
1	13, male	Abdominal cramps (8 weeks) with acute worsening, weight loss	MRI: thickened terminal ileum, 2nd US: suspected Meckel diverticulum	1. Intussusception: Pneumatic reduction 2. Intussusception: Pneumatic reduction unsuccessful, laparotomy and ileal segment resection, detection of an intramural discoid tumor	Ileal segment resection (16 cm, 60 cm prox. Bauhin)	Burkitt lymphoma, C-MYC positive LDH < 500 U/l Polyp, 3 × 2.9 × 0.8 cm, complete resection	I	B-NHL BFM 04, R1 (two cycles) +Rituximab window	1.5
2	16, female	Abdominal cramps (3 weeks), minimal weight loss, night sweats, intermittent nausea	CT/US: excentric thickening of bowel wall terminal ileum, enlarged lymphnodes	1. Intussusception: Pneumatic reduction 2. Intussusception: Incomplete hydrostatic and pneumatic reduction	US-guided percutaneous biopsies ileo-cecal	Diffuse large B cell lymphoma, C-MYC negative, LDH < 500 U/l PET-CT scan: 52 × 48 mm, cc 50 mm FDG-positive tumor ileocecal and local lymphnodes	III	B-NHL BFM 2013 R2 (four cycles) +Rituximab window	2.5
3	6.5, male	Abdominal cramps (6 weeks) with acute worsening, intermittent bilious emesis, weight loss	US: no suspicion	Hydrostatic reduction not successful, therefore, laparotomy with manual reduction ileo-colic intussusception and ileal segment resection of an ileo-ileal intussusception	Ileal segment resection (10 cm, 40 cm prox. Bauhin)	Burkitt lymphoma, C-MYC positive, LDH > 500 U/l Ileal resection with nodular infiltration of lymphoma, incomplete resection, local lymphnode-involvement	III	B-NHL BFM 2004 R3 (six cycles)	7

Table 1 (continued)

Patient No	Age (years), sex	Presenting symptoms	PLP diagnosis	Surgical therapy	Biopsy/resection	Histology/tumor size/staging	Stage (St. Jude)	Chemotherapy/risk group	Follow-up (years)
4	6 3/4 years, female	Abdominal pain (4 weeks), bloody diarrhea, leg pain	US: ileocolic intussusception, thickened ileal bowel wall, hepatic lesions MRI: ileocecal tumor, hepatic lesions	Hydrostatic reduction partially successful	US-guided percutaneous biopsy	Burkitt lymphoma, C-MYC positive, LDH > 1000 U/l MRI: tumor right lower abdomen (5 cm diameter), multiple liver metastases, lymph node enlargement, bone marrow infiltration, pleural effusions Bone-marrow: 85% infiltration of Burkitt lymphoma	IV	B-NHL BFM registry 2012 R4 (six cycles)	5.5
5	3 years, male	Abdominal pain (3 days), diarrhea, emesis	US: thickened terminal ileum MRI: tumor in terminal ileum	Pneumatic reduction: intussusception not confirmed	US-guided percutaneous biopsy	Burkitt lymphoma, C-MYC positive, LDH < 500 U/l MRI: Tumor terminal ileum 9.5 × 7 × 6 cm, local mesenteric lymph nodes involved	II	B-NHL BFM registry 2012 R2 (four cycles)	5

PLP pathological lead point, US ultrasound, C-MYC positive break in C-MYC gene on chromosome 8q24 by interphase FISH, indicative for translocation (8;14), B-NHL B-cell non-Hodgkin Lymphoma, BFM Berlin–Frankfurt–Münster group

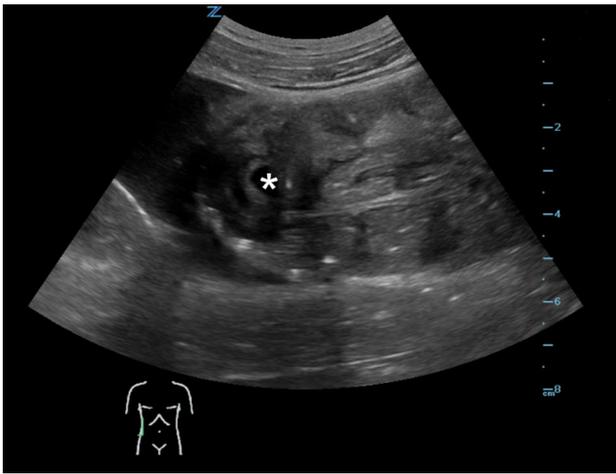


Fig. 1 Ultrasound image showing a cystic structure (asterisk) within the intussusception which was thought to be a Meckel diverticulum



Fig. 2 Intraoperative documentation of a discoid tumor of 2×2 cm diameter 60 cm proximal of the ileo-cecal valve which acted as lead-point

the group of mature aggressive B-NHL accounts for 50% of NHL and comprises Burkitt-lymphoma and Burkitt-leukemia, diffuse large B-cell lymphoma (DLBCL), and rarely not further specified mature aggressive B-NHL [10]. The association between lymphoma and intussusception was first made by Wayne et al. more than 40 years ago [3]. Since then, the therapeutic approach and outcome for patients with intestinal lymphoma has changed drastically: surgery used to be the mainstay of therapy. With modern chemotherapy-regimens and risk stratification excellent outcome can be expected even for patients with high-stage malignant disease. Therefore, surgery is currently reserved for complications, such as irreducible intussusception or diagnostic procedures. The long-term survival for children with Burkitt's lymphoma used to be below 60% and only 40% in patients with incomplete or no resection [14]. Nowadays in children with aggressive B-NHL the 5-year-survival-rate is above 90% with chemotherapeutic treatment alone [10, 15].

Therefore, many new questions arise in respect to the role of surgery in these patients, as well as the question of diagnosis of PLP in intussusception.

Clinical differentiation between an idiopathic intussusception and a PLP as cause of the intussusception can be challenging. The most important clue is the patient's age with older children having a clearly increased risk of having a PLP. Blakelock et al. found that over 50% of patients presenting with an intussusception beyond the age of 5 years had a PLP, in Ong's et al. series this same result was found already beyond the age of 4 years [1, 2]. Looking specifically at the risk of lymphoma as a PLP age is also a valuable indicator: in Gupta et al's series the mean age of patients presenting with intussusception due to intestinal lymphoma was 10 years (range 3–10) and in England et al's series the same patients mean age was 6 years (range 2–11) [11, 12]. As shown in our series, another clue may be the longer duration of symptoms compared to idiopathic intussusception as well as additional clinical features, such as weight loss or night sweats, as specific clues for a neoplastic disease [16, 17]. Laboratory tests are rarely helpful in differentiating idiopathic intussusception from neoplastic PLP. However, serum lactate dehydrogenase (LDH), an enzyme, which is elevated in case of tissue damage or in malignant disease with high cellular turnover, is used as a marker for lymphoma. The elevation of LDH is neither specific nor sensitive for lymphoma and in more than 50% of patients presenting with B NHL, LDH is normal [18]. Nevertheless, in some cases measurement of LDH may be a helpful marker of lymphoma, especially in higher stage disease. Not, however, in stage I and II disease, as LDH is not necessarily elevated, as we could see as well in our patients. Correlation between elevated LDH and poor prognostic outcome of NHL is in discussion and in some treatment protocols LDH levels guides risk stratification. [10, 18]. Recurrence of idiopathic intussusception is common and most recurrences will numerically occur in this patient group. Yet the recurrence rate is higher in patients with a PLP, so this too may be an indicator thereof [19, 20].

Moving on to the question of treatment, it has been questioned if a conservative reduction attempt should even be made in older children with an intussusception due to their high likelihood of having a PLP and the small percentage of successful reduction rates in these patients [1, 3, 11, 16, 17]. In our series three patients were treated with conservative reduction alone avoiding the morbidity of laparotomy. In one of the two surgically treated patients, ileal resection could possibly have been avoided, if imaging would have been repeated after the unsuccessful first reduction attempt, as this patient had double invagination and enlarged lymph nodes. In this patient, resection remained incomplete and was, therefore, of no benefit in regard to staging. In addition, start of chemotherapy had to be postponed for 1 week to allow wound healing. This is in contrast to our case 1,

where complete resection of a small intramural Burkitt-lymphoma—which was not clearly detectable by ultrasound, colonoscopy or MRI—lead to downstaging, and thus surgery was beneficial for this patient. No complications of reductions, pneumatic or hydrostatic, were seen in our patients. With this and recent literature in mind, it seems justified to attempt a conservative reduction even in older children or in children with suspected PLP in the absence of contraindications such as peritonitis [2, 16].

This leads to a vital next question: can a PLP be missed if pneumatic or hydrostatic reduction is successful? Most institutions, like ours, perform an ultrasound to confirm diagnosis of intussusception before reduction. Ultrasound may be investigator-dependent, but nonetheless it is useful in depicting PLP [20, 21]. Navarro et al. showed that in two-thirds of cases with PLP, an abnormality can be found on ultrasound and in half of these the actual diagnosis was made sonographically [22]. In our series, in all but one patient, the presence of a PLP was suspected by ultrasound. As of yet, no consensus exists on how to proceed if ultrasound and the reduction enema fail to document a PLP, yet the clinical suspicion of existence thereof remains high. In our opinion, a high index of suspicion in school-aged patients in absence of a PLP must lead to further investigations with CT or MRI and, if not conclusive, even to surgical exploration. The presence of malignant PLP has to be ruled out actively as we experienced in Patient 1, where MRI was not conclusive, but recurrent intussusceptions necessitated surgery finally leading to the correct diagnosis of a discoid intramural lesion with only 8 mm thickness.

Even though chemotherapy is the treatment of choice in B-NHL, as many as 50% of patients with abdominal disease still undergo urgent laparotomy at some point due to acute abdominal symptoms caused by intestinal obstruction, appendicitis or intussusception [13, 23, 24]. In fact, these patients may even have a better prognosis compared to patients without, e.g. intestinal obstructive symptoms, since it may lead to earlier diagnosis of these rapidly growing tumors [12]. If a tumor suspicious of lymphoma is detected during explorative surgery and complete resection is feasible, it is recommended, as complete resection of a tumor will downgrade the staging and, therefore, lead to lower risk stratification with reduced chemotherapy [10]. However, extended or even mutilating surgery should be avoided due to the favorable outcome despite advanced local tumor stage, as well as the fact that surgical complications may delay the begin of chemotherapy, which is clearly the more important treatment modality [10, 12, 13]. In B-NHL, chemotherapeutic treatment is indicated even in patients with R0 resection, yet with lower intensity [10]. It is important to be aware that complete resection will lead to downstaging only from stage II to stage I B-NHL. Therefore, it is important to perform local lymph node exploration and resection of

involved lymph nodes for staging reasons. If lymph nodes are involved, complete resection of the intestinal lymphoma does not improve outcome or lead to reduced intensity of chemotherapy.

In stage III lymphoma (i.e. extensive intraabdominal disease) lymph node resection is not indicated and the aim of surgery from an oncological perspective is diagnostic biopsy.

Finally, the question of the role of minimal-invasive surgery must be asked. It has been shown that laparoscopy is a safe alternative to open surgery for intussusception in skilled hands. Recent advances in minimally invasive surgery have resulted in high reduction rates, low complication rates, low overall postoperative morbidity, and a shorter length of stay in the hospital compared with those noted with use of the open surgical approach [25–27]. However, Ntoulia et al. showed in their study that of 427 children with intussusception 74 needed a surgical approach and only 36% underwent laparoscopy. They had 3 patients with Burkitt's Lymphoma. All of them underwent laparotomy [21]. Higher conversion rates to due existence and simultaneous treatment of PLPs must be considered, as well as possibly missing a PLP due to the missing tactile cues in laparoscopy [27, 28].

In conclusion, the lessons we learnt from these patients is that a high index of suspicion for PLP in children older than 4 years and children with recurrent intussusception is necessary. Malignant, highly aggressive B-NHL, although rare, must actively be searched for. Pneumatic or hydrostatic reduction should remain the first line treatment in most cases, even in older children or those with suspected PLP. If surgery is necessary, disabling surgery should be avoided due to excellent prognosis of intestinal B-NHL with appropriate chemotherapeutic treatment alone.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by our local ethics committee.

Informed consent Informed consent was given by all patients.

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