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Invasive non-typhoidal *Salmonella* infection complicated by metastatic infections: Report of three cases



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ABSTRACT

Non-typhoidal Salmonella (NTS) disease is usually a self-limiting infection presenting with digestive symptoms. However, disseminated presentation with involvement of secondary infectious sites is observed. We report diagnostic specificities and challenges related to the management of three patients with invasive NTS (iNTS) and secondary infectious locations. Among the seven patients (age range 46 - 83 years), four (two with extra-digestive infectious sites) had at least one immune debilitating condition. Two patients were incidentally discovered with iNTS and deceased after developing a septic shock despite antimicrobial treatment. Two individuals recovered under medical treatment without complications. Three other patients presented with secondary infectious sites. Case 1 suffered from urinary tract infection and dorsolumbar spondylodiscitis that responded well to antimicrobials and surgery. Abdominal prosthetic aortic aneurysm was diagnosed in case 2 and medical treatment only was applied. After four years of follow-up, he remains under antimicrobial treatment. Case 3 presented with conjoint thoracic aortic aneurysm and cutaneous abscesses managed with antimicrobials and surgery. Atherosclerosis and previous vascular intervention were the predisposing events for vascular involvement. iNTS is a serious disease carrying a high risk of mortality or secondary locations. Secondary locations can be managed by long duration antimicrobial therapy combined with surgery. Spine and aortitis are the most frequent secondary locations. Multi-drug resistant NTS represent an additional risk of mortality. Public health measures should be implemented to limit the spread of NTS to humans and the emergence of drug resistance.

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Introduction

Salmonella species are gram-negative Enterobacteriaceae divided into two major groups: typhoidal Salmonella (TS) (S. Typhi and S. Paratyphi A, B and C) and non-typhoidal Salmonella (NTS) comprising over 2500 serotypes. TS are hosted by humans and spread through oro-fecal transmission [1]. NTS are hosted by animals and spread as foodborne pathogens, direct contact with wild animals and pets (including reptiles) or oro-fecal inter-human transmissions. NTS related infections usually present as a self-limiting diarrhea not requiring antimicrobials [1,2]. In this form of the disease, antimicrobial management may not shorten the duration of diarrhea but might



Tablee 1 Description (

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<i>iella</i> disease diagnosed during th	Travel history
invasive non-typhoidal salmon	Co-morhidities
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Description	Datient Aor

Patient Age, years	Age, years	Sex	Context of admission Co-morbidities (duration of symptoms)	Co-morbidities	Travel history	Stool exam	Blood culture	Secondary infection site	Treatment and evolution
Case 1	66	Male	Back pain, mictalgia, pollakiuria, light sweating and anorexia (3 weeks)	COPDRA under methylprednisolone	None	Not available	S. Enteritidis#	Urinary tract Dorsal and lumbar spines (spondylodiscitis)	Total antimicrobial treatment 15 weeks Surgical management Infection control after 14 weeks
Case 2	79	Male	Fever, chills and diarrhea (3 days)	Aortoiliac aneurysm Embolization of hypogastric aneurysm	Return from SSA	S. Enteritidis	S. Enteritidis	Hypogastric mycotic aneurysm	Optimal infectious control under antimicrobials Ongoing treatment (4 years follow-up) No surgical management
Case 3	64	Female	Multiple bilateral abscesses of the thighs (5 weeks)	Myasthenia gravis under azathioprine and methylprednisolone Type 2 diabetes mellitus Radiofrequency ablation of varicose veins	None from the patient *	S. Typhimurium	S. Typhimurium	Subcutaneous and cutaneous Mycotic aortic aneurysm	Surgical resection of aortic aneurysm and pericardial patch Eight weeks course of antimicrobials Systemic infectious Control with persistent positive rectal swab
Case 4	73	Male	Elective post tibio- popliteal bypass surgery - Incidental finding (5 days post- surgery)	Type 2 diabetes mellitus ESRD	Residence in SSA the previous year	.S. Rissen	S. Rissen	None identified	Antimicrobial treatment Dead as a result of septic shock at day 11
Case 5	83	Male	NSTEMI - Incidental finding (4 days after admission)	Not known	None	S. Typhimurium	S. Typhimurium S. Typhimurium None identified	None identified	Antimicrobial treatment Dead as a result of septic shock and spontaneous pneumothorax at the ICU at day 10
Case 6	46	Male	Diarrhea and abdominal pain (10 davs)	Digestive (pancreatic) adenocarcinoma under chemotherapy [§]	None	Not available	S. Typhimurium	None identified	Optimal infection control under antimicrobial treatment
Case 7	38	Male	Diarrhea and abdominal pain (2 days)	None	None	S. Typhimurium	S. Typhimurium S. Typhimurium None identified	None identified	Optimal infection control under antimicrobial treatment
# Also pre: chronic ob	sent in u structiv€	rinary samp ? pulmonary	ole, * The son of the patier y disease, RA: rheumatoid	* Also present in urinary sample, * The son of the patient returned from Asia few months prior to the presentation and beginning of the current illness. Attempts to test the son were unsuccessful, [§] Gemcital chronic obstructive pulmonary disease, RA: rheumatoid arthritis, SSA: Sub-Saharan Africa, ESRD: end stage renal disease, NSTEMI: non-ST segment elevation myocardial infarction, ICU: intensive care unit.	presentation and dise	beginning of the cu ase, NSTEMI: non-S	rrrent illness. Atten T segment elevatio	npts to test the son were uns n myocardial infarction, ICU:	* Also present in urinary sample, * The son of the patient returned from Asia few months prior to the presentation and beginning of the current illness. Attempts to test the son were unsuccessful, [§] Gemcitabine and oxaliplatine, COPD: chronic obstructive pulmonary disease, RA: rheumatoid arthritis, SSA: Sub-Saharan Africa, ESRD: end stage renal disease, NSTEMI: non-ST segment elevation myocardial infarction, ICU: intensive care unit.

promote long term carriage and induce emergence of drug resistance [3]. NTS are among the four most prevalent causes of diarrhea worldwide, mostly in Africa and Asia. In up to 5% of cases, it presents as an invasive NTS (iNTS) disease with bacteremia (with or without diarrhea) thus requiring antimicrobial treatment [4]. Risk factors for developing iNTS include extreme ages, immunodeficiency including HIV/AIDS, co-morbidities such as diabetes or cancer, malnutrition, malaria, and sickle cells disease [1,4].

Secondary septic locations occur in 30–40% of patients with iNTS and affect bones, joints and soft tissues, urinary system, lungs and pleura, neuro-meningeal system, and endovascular graft, among others [5]. We report a series of patients affected by iNTS and describe three of them presenting with secondary infectious localizations.

Cases presentation

From January 2017 to June 2020, we identified seven patients presenting with iNTS infection at the University Hospital Brugmann, Brussels (Table 1). Six patients were male and the age of the overall population ranged from 46 to 83 years. Four patients presented with complaints of less than a week (range 3-5 days). Two patients presented isolated fever and were admitted for non-infectious conditions including non-ST segment elevation myocardial infarction and post-operative follow-up at the intensive care unit after tibio-popliteal bypass surgery. Three other patients reported abdominal pain and/or diarrhea with or without fever. The last two patients reported urinary symptoms and multiple abscesses of the thighs on admission (Table 1). Among our patients with iNTS, two died shortly after diagnosis, three had a secondary location, and two had an uncomplicated bacteremia. Salmonella enterica serovar Typhimurium was the most common organism isolated in four patients, followed by Salmonella enterica serovar Enteritidis (two patients). One patient was identified with Salmonella enterica serovar Rissen. Patients with secondary infectious localizations namely urinary tract infection plus spondylodiscitis (Case 1), abdominal prosthetic aortic aneurysm (Case 2), and thoracic aortic aneurysm and cutaneous abscesses (Case 3), are further described in the present report.

Case 1

A 66-year-old man presented at our emergency department (ED) with lower back pain for three weeks, mictalgia, pollakiuria, night sweating and anorexia. He had no recent travel history. Past medical history included hypertension, chronic obstructive pulmonary disease and rheumatoid arthritis treated by methylprednisolone. On examination, temperature was 37.3 °C, blood pressure 107/ 85 mmHg, heart rate 90 beats per minute, oxygen saturation 96% at room air and respiratory rate 20 breaths per minute. Positive physical examination findings included lower abdominal pain without tenderness nor guarding and bilaterally painful costolumbar angles. Initial laboratory findings are shown in Table 2. Beside the systemic biological inflammatory state, an initial alteration of liver function tests and renal function were observed. Urine analysis as well as blood collection for cultures were done and the patient was empirically started on intravenous cefuroxime for a presumptive urinary tract infection. Blood and urine cultures came back positive for Salmonella species, later identified as Salmonella Enteritidis sensitive to usual antimicrobials except cefuroxime. Stool culture was not performed. Cefuroxime was shifted to ceftriaxone then to oral cotrimoxazole. However, because of persistent fever after 10 days of treatment, a computed tomography (CT) scan was performed and revealed vertebral lesions in Th12-L1, L3 and L5 suggestive of discitis with tomodensitometric stigmata of instability. This was confirmed by magnetic resonance imaging (Figs. 1 and 2, A-B-C). At week 14

Table 2

Initial biologica	l parameters of	patients with	secondary	septic sites.
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Biological parameters	Case 1	Case 2	Case 3
Hemoglobin, g/dL	13.1	9.9	12.4
White blood cells, 10 ³ / µl	8.16	8.30	8.49
Platelets, 10 ³ /µl	120	327	333
C-reactive protein, mg/L	169	335	81
Urea, mg/dL	112	98	43
Creatinine, mg/dL	1.46 *	2.36	0.79
eGFR, ml/min/1.73 m ²	49	25	79
AST, IU/L	63	89	16
ALT, IU/L	72	67	20
GGT, IU/L	276	227	53
ALP, IU/L	288	263	72
Lipase, IU/L	10	126#	74#
Plasma glucose level, mmol/L* *	8.05	7.38	26.36
HbA1c, mmol/mol	45	na	107

eGFR: estimated glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma glutamyl-transpeptidase, ALP: alkaline phosphatase, IU: international unit, HbA1c: glycated hemoglobin, na: not applicable, *baseline value 0.86 mg/dL and optimal correction after infection control, # without signs of pancreatitis at tomodensitometric examination, ** random value.



Fig. 1. Sagittal bone window reconstruction from an abdominal CT scan. Multiple vertebral fractures (T11, T12, L1, L3, L5) with lysis of the vertebral bodies of T11, T12 and L1 (arrows).

post-admission, after optimal infection control (Fig. 2 D-E-F), chirurgical stabilization of the spine was conducted and the patient was advised to wear a SpinoMed® corset for one year. Subsequent imaging showed improvement of collections. The microbiologic examination of the paravertebral collection did not show the presence of bacteria. A dual therapy with cotrimoxazole and ciprofloxacin was administered for 15 weeks. The patient underwent five months of rehabilitation prior to discharge. He remained stable and no recurrent disease was observed up to 15 months after rehabilitation.

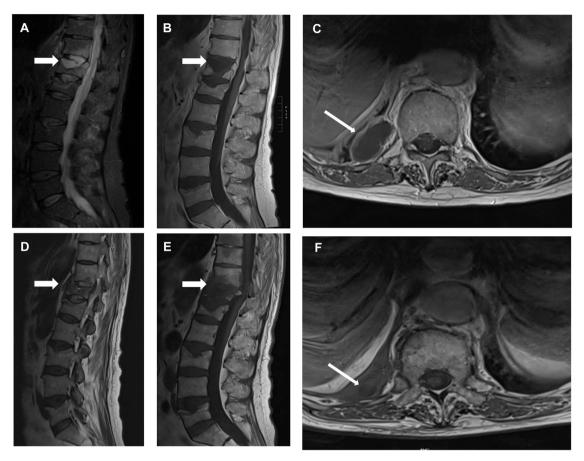


Fig. 2. Spine MRI sagittal STIR, sagittal and axial T1 weighted images after gadolinium injection before (A, B and C, respectively) and after (D, E and F, respectively) medical treatment and before surgical management. Spondylodiscitis T12-L1 with destructive discovertebral collection (thick arrow) and right paravertrebral collection (thin arrow).

Case 2

A 79-year-old male patient presented with fever, chills, and diarrhea upon return from Democratic Republic of Congo three days prior to the consultation at the ED. His past medical history included high blood pressure, and endovascular prosthesis after embolization of a left hypogastric aneurysm within the preceding two years. On first examination, his pulse was 125 beats/min, blood pressure was 120/67 mm Hg, temperature 38 °C, capillary oxygen saturations 98% at room air and his respiratory rate 20/min. Initial examination at the ED was unremarkable. Initial laboratory findings are depicted in Table 2. Complete blood count showed an hypochromic microcytic anemia with iron deficiency, elevated urea and creatinine levels, elevated cholestatic liver enzymes as well as a high lipase level. Sensitive Salmonella Enteriditis grew in the blood and in the stool culture. Abdominal CT scan (Fig. 3 A-B) and leukocyte scintigraphy (not shown) revealed a collection around the vascular prosthesis localized in the left common iliac artery and another one at the hypogastric region suggestive of mycotic aneurysm. The patient was initially empirically treated with intravenous ceftriaxone 2g once daily and at day seven of treatment, oral conventional dose of ciprofloxacin was provided for a duration of six weeks while the patient was admitted. Surgical treatment was not retained due to major risk associated to the procedure. He was discharged with oral ciprofloxacin and a control imaging study was scheduled after three months of treatment (i.e. after six additional weeks ambulatory treatment). A positron emission tomographic (PET) scan (after three months) showed unfavorable evolution of the periaortic lesions with increasing gas component. A combination therapy using cotrimoxazole and ciprofloxacin was initiated. Three months later, an angiotomodensitometry showed persistent local inflammatory lesions at the site of vascular prosthesis. A multidisciplinary decision was taken in line with further antimicrobial treatment. The double antimicrobial treatment was continued up to three years after which only cotrimoxazole was continued until year four at the time of this report. Clinically, the patient remained in good condition and C-reactive protein normalized.

Case 3

A 64 year-old woman presented with persistent multiple abscesses of both thighs, evolving for five weeks before consultation at the ED. Four years before, the patient underwent radiofrequency ablation and phlebotomy to manage bilateral recurrent varicose veins. Even though the patient did not report any travel history, her son did return from India a few months prior to the onset of the symptoms. Her son refused to provide any sample for stool culture. She reported generalized myasthenia gravis treated with azathioprine and methylprednisolone the last four months preceding the admission, high blood pressure, hypercholesterolemia and type 2 diabetes mellitus.

On admission, she was afebrile. Tachycardia was noticed but she remained otherwise hemodynamically stable. Physical examination revealed several abscess on the inner face of both thighs. Laboratory investigation revealed a systemic inflammatory reaction, hyperglycemia in the context of uncontrolled diabetes mellitus (HbA1c 11.9%), Table 2. PET scan demonstrated not only multiple cutaneous and subcutaneous abscesses in the lower limbs and the anterior abdominal wall but also an infiltration of mediastinal fat at the vicinity of the aortic arch with adjacent left pulmonary hilar lymphadenopathy suggestive of early mycotic aneurysm. Angiotomodensitometry confirmed the presence of a pseudo-aneurysm of

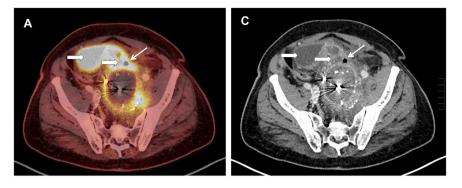


Fig. 3. PET and CT scan fusion (A) and abdominal CT scan after injection of contrast media (B) axial views. Abdominal aortic aneurysm with endograft surrounded by multiple infective collections (thick arrow). Gas bubbles within a periaortic collection (thin arrow).

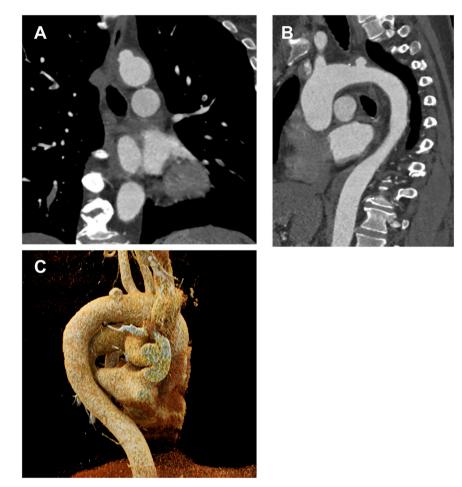


Fig. 4. CT angiography coronal (A) and parasagittal (B) views and Volume Rendering Technique reconstruction (C). Saccular aneurysm of the transverse aortic arch.

the aortic arch, located near the emergence of the left subclavian artery (Fig. 4). Cultures from both the cutaneous abscesses, stool examination (two days later) and blood isolated multi-drug resistant (extended-spectrum β -lactamases – ESBL) *Salmonella* Typhimurium. Initial treatment with intravenous temocilline 2 g twice daily was started based on antimicrobial sensitivity of the bacteria. After five days of treatment, given the persistence of bacteremia and pyrexia, meropenem 2 g three times a day replaced temocilline. A new angiotomodensitometry performed at weeks five of hospitalization showed a larger pseudo-aneurysm with new features of a saccular aneurysm (Fig. 4). Resection of the aneurysm with pericardial patch plasty was performed. After surgery, no post-operative complication was observed and the patient remained afebrile with progressively declining inflammatory markers. Intravenous antimicrobial therapy was continued for a total duration of eight weeks overall and stopped. About five months after discharge the patient remained free of any residual symptom, and repeated blood tests ruled out ongoing inflammatory reaction. A control thoracic CT-angiography was negative for any active pathological vascular lesion. However, her epidemiological rectal swab was still positive for *Salmonella* Typhimurium. A PET-scan performed 36 months after therapy showed no more active lesions.

Discussion

In this report, we describe a single center set of patients admitted with iNTS within a period of 30 months. The presence of positive blood cultures plus or minus stool samples for NTS was ascertained in seven patients. Among those, three had secondary infectious sites and were further described in detail. The first patient presented with urinary tract infection and spondylodiscitis and combination of medical treatment and surgery achieved good treatment response. The second patient was diagnosed with abdominal prosthetic aortic aneurysm. He was treated with life-long antimicrobials because of high surgical risk. The last patient was admitted with thoracic aortic aneurysm and cutaneous abscesses that responded well to antimicrobial treatment and surgery.

All three patients presented with immune depressing conditions or treatments (myasthenia gravis under immunosuppressive agents, diabetes mellitus, end stage renal disease) and/or previous vascular surgery. This is consistent with the observations from previous reports suggesting a higher incidence of iNTS among individuals with depressed immunity [6]. *Salmonella* is a rare cause of hematogenous osteomyelitis. It represents less than 1–7% of all osteomyelitis and it complicates iNTS in about 1–5% of cases [5,7]. Differential diagnosis includes Pott's disease. Diagnosis is made by culture of a bone biopsy. In Case 1, concomitant appearance of a spondylodiscitis on lumbar CT scan and positive blood cultures for *Salmonella* spp supported the diagnosis. Besides the medical treatment, the place of spine immobilization to avoid neurological complications shouldn't be underestimated [7].

Case 1. presented with signs and symptoms of upper urinary tract infection confirmed by positive urine sample analysis for *Salmonella* Enteritidis that comforted the diagnosis. Urinary tract infections (UTI) are often associated with urinary tract abnormalities, chronic pyelonephritis, nephrolithiasis and immune suppression [8]. It represents less than one percent of secondary locations and can be ascendant or can occur via hematogenous spread [9]. Our patient had not only immune debilitating conditions but also a small nephrolithiasis in the left kidney.

The two patients with vascular involvement were at risk based on their comorbidities including previous aortoiliac aneurysm and atherosclerotic vascular disease due to diabetes mellitus. Mycotic aneurysm of the aorta is a potentially life-threatening disease and develops quite exclusively on pre-existing lesions like atherosclerotic plaques, surgery, trauma, or by extension from a contiguous abscess [10,11]. NTS represent a substantial 40% of all causative organisms [12]. Because of the preponderance of vascular lesions with aging, about 25% of patients above 50 years old, presenting with iNTS will develop aortitis [12]. The NTS vascular infection (NTSVI) score has been proposed by Po-Lin et al. to assess the risk of developing a mycotic aneurysm in a Taiwanese population. They report male gender, hypertension, coronary arterial disease, and serogroup C1 infections as positive predictors for vascular graft. However, their data suggest that malignancy and immunosuppressive therapy might rather be negative predictors of vascular infectious engraftment [13]. A protective effect of immune suppression is somewhat contra-intuitive since it has been associated with a greater risk for iNTS. These findings need to be checked in an independent population to confirm their external validity. As expected, the same authors found that a high calcium score of the aorta was associated with an increased risk for aortitis. A retrospective study of aortic graft infection in 142 patients revealed that surgery was associated with a very high morbidity, re-operation risk and mortality. In critical cases, one could therefore rely on antimicrobials to minimize the risk related to surgery. This was the case of the second patient discussed in the present report [14]. In this patient, the course of antimicrobial treatment continues up to four years after the initial diagnosis. This scenario is divergent from that of the third patient who was eligible for surgery, had a smooth post-operative evolution and completed the antimicrobial treatment at week 15.

Pyomyositis is seldom reported [15] and mostly related to *Salmonella* Enteritidis. Local trauma is considered to be the

predisposing condition. The psoas muscle is most frequently affected. In Case 3, multiple abscesses of the thighs were observed during clinical examination and at imaging studies. Considering the past medical history of radiofrequency ablation of varicosities of lower limbs, and despite the lag time of about four years, this could be, in our view, considered as the main predisposing factor in this patient.

NTS are carried in the intestinal tract which may reflect asymptomatic carriage or following recovery from asymptomatic disease; the carriage may last various durations (chronic carriers). In our series, five out of seven patients had a positive stool culture (not performed in two patients). In a review of the effect of antimicrobial therapy on NTS illness, antimicrobials didn't improve symptoms' duration but increase carriage in two-third of patients compared to one-third in placebo treated patients [3]. In Case 3, stools were still positive on day 73 after diagnosis while she received eight weeks of intravenous antimicrobial therapy.

Alarmingly, an increasing proportion of NTS has acquired antimicrobial resistance, mainly due to antimicrobial abuse in animal husbandry [16,17]. Case 3 had a resistant extended ß-lactamase producing *Salmonella* which required an eight-week duration treatment with meropenem after failure of temocillin. In a 2019 series of NTS in Taiwanese children, 31% were resistant to quinolones, 6% to third generation cephalosporin due to extended spectrum ß-lactamases, and 14% considered as MDR: resistant to more than three antimicrobial classes [18]. Antimicrobial resistance negatively affects treatment outcome increasing the mortality rate about four times [19].

Conclusion

Non-typhoidal salmonellosis bacteremia carries a poor prognosis as out of seven reported patients, two died and three developed secondary septic locations leading to prolonged therapy and surgery. One in seven had a multidrug resistant NTS. More attention should be paid to public health measures to limit the spread of NTS among humans: i.e. hand hygiene, healthy cooking. Antimicrobial stewardship should be promoted to prevent the development of antimicrobial resistance: i.e. antimicrobials in agriculture and veterinary care. An efficacious and effective vaccine against NTS is also eagerly awaited.

Data availability statement

All data related to the cases described in the present manuscript are available upon request from the corresponding author.

Funding statement

None.

Ethical Approval and consent to participate

The three individuals who presented metastatic septic locations gave their written informed consent to be included in the present report. A waiver for informed consent was obtained from our institutional ethics review board for the four other patients since their data were retrospectively consulted as an overview of the overall patients' population with iNTS.

CRediT authorship contribution statement

Mariana Dumitru Taliha, Eric Balti, Philippe Clevenbergh: Conception and design, Acquisition of data or analysis and interpretation of data, Drafting the article, Agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved. Mariana Dumitru Taliha, Eric Balti, Evelyne Maillart, Sophie Leemans, axime Taghavi, Sergiu-Andrei Carausu, Said Sanoussi, Bhavna Mahadeb, Philippe Clevenbergh: Revising it critically for important intellectual content, Final approval of the version published.

Conflicts of Interest

None declared.

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