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Original contribution

Polyvinylpyrrolidone deposition disease in patients with intravenous opioid use: a case series☆,☆☆,☆☆☆

Friedemann Leh MD [a], Ida Viken Stalund MD [a,b,*], Tormod Karlsen Bjånes MD, PhD [c], Christian Ohldieck MD [d], Einar Svarstad MD, PhD [b], Sabine Leh MD, PhD [a,b]

[a] *Department of Pathology, Haukeland University Hospital, Jonas Lies Vei 65, Bergen, 5021, Norway*
[b] *Department of Clinical Medicine, University of Bergen, Jonas Lies Vei 87, Bergen, 5021, Norway*
[c] *Department of Medical Biochemistry and Pharmacology, Haukeland University Hospital, Jonas Lies Vei 65, Bergen, 5021, Norway*
[d] *Department of Addiction Medicine, Haukeland University Hospital, Jonas Lies Vei 65, Bergen, 5021, Norway*

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Summary The polymer polyvinylpyrrolidone (PVP) is an excipient widely used in prescription drugs. Depending on the molecular weight (MW), parenterally administered PVP may accumulate in various tissues. Consequently, moderate and high MW PVP have only been used in oral preparations since the late 1970s. Surprisingly, starting in 2009, pathology departments in Norway received biopsies revealing PVP deposition, all from patients with a history of intravenous drug use. We identified 13 patients with PVP deposition and re-evaluated 31 biopsies and two autopsies. Common indications for biopsy were renal insufficiency, anemia, pathological fractures, and abdominal complaints. We observed PVP deposits in all biopsies (kidney, hematopoietic bone marrow, bone, gastrointestinal tract, lymph node, and skin) and all sampled tissue from the autopsies. Overall, the clinical findings could be related to PVP deposits in the biopsies. In the most seriously affected patients, PVP deposition caused severe organ dysfunction and contributed to the fatal outcomes of two patients. All patients except for one were prescribed opioid substitution drugs (OSDs), and most of the patients admitted to having

Abbreviations: PVP, polyvinylpyrrolidone; MW, molecular weight; OSD, opioid substitution drugs; H&E, hematoxylin and eosin; PASM, periodic acid silver methenamine; IQR, interquartile range; PAS, Periodic acid–Schiff; IFTA, interstitial fibrosis and tubular atrophy.

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* Corresponding author. Department of Pathology, Haukeland University Hospital, Post Box 1, Bergen, 5021, Norway.
E-mail addresses: friedemann.leh@helse-bergen.no (F. Leh), ida.viken.stalund@helse-bergen.no, ida.stalund@uib.no (I.V. Stalund), tormod.karlsen.bjanes@helse-bergen.no (T.K. Bjånes), christian.ohldieck@helse-bergen.no (C. Ohldieck), einar.svarstad@uib.no (E. Svarstad), sabine.leh@helse-bergen.no (S. Leh).

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injected such medications. Several OSDs contain PVP. One methadone formulation that was marketed in Norway from 2007 to 2014 contained large amounts of very high MW PVP, making it the most likely source of PVP deposition. Although the presumed source of PVP in these patients has now been withdrawn from the market, pathologists should be aware of PVP deposits when evaluating biopsies from this patient group.

1. Background and introduction

Starting in 2009, pathology departments in Norway received an increasing number of diagnostic biopsies showing deposits of polyvinylpyrrolidone (PVP). All patients had a background of opioid addiction, and the majority received opioid substitution therapy.

PVP is a polymer of vinylpyrrolidone. It is widely used as an excipient in tablets and other oral medications [1]. It is neither absorbed from the gastrointestinal (GI) tract nor degraded enzymatically. If injected, elimination is only possible by renal excretion [2]. While PVP of low molecular weight (MW) will be completely excreted, high MW PVP will accumulate in the body's tissues [2]. Over time, and with an increasing dose of PVP, this accumulation can cause clinically relevant organ damage [3]. In the middle part of the last century, PVP was used as a plasma expander and as a retarding agent in injectable hormonal substitution drugs [3]. Because of the discovery of PVP deposition, high MW PVP has not been used in parenteral preparations since the end of the 1970s, at least not in the Western world [3].

Therefore, we were surprised to find PVP deposition in tissue biopsies from 2009 onward. The fact that all patients had a history of opioid addiction and intravenous drug use led us to suspect opioids as a likely source of PVP. The patients had known access to opioid substitution drugs (OSDs). Although OSDs are designed for oral administration, intravenous use is widespread among persons who inject drugs [4,5]. Several OSDs contain PVP [6]. Consequently, these medications represented a possible source for the observed PVP deposition.

The present study has two aims: (1) to describe the clinical and pathological findings related to PVP deposition and increase awareness of this nearly forgotten disease and (2) to explain the occurrence of PVP deposition disease among patients in Norway with a history of intravenous opioid use.

2. Material and methods

2.1. Patients

Patients (n = 13) with PVP deposition were consecutively and retrospectively identified by diagnostic biopsies received at the Department of Pathology at Haukeland University Hospital in Bergen, Norway. The biopsies were received between 2009 and 2013. Clinical data, including drug history, the prescription of OSDs, and laboratory data, were obtained from the referral forms and the patients' medical records. Patient survival was followed until 2020. Two autopsies were available for investigation. The clinical course and findings for one of the included patients were recently published in a case report by the authors [7]. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK 27687).

2.2. Microscopy

Formalin-fixed biopsies and tissue samples from the autopsies were paraffin embedded and sectioned according to standard methods. The diagnosis of PVP deposition was made on hematoxylin and eosin (H&E)-stained sections based on the characteristic histological appearance of the deposited material. In addition, sections with PVP deposits were stained with Congo red and periodic acid silver methenamine (PASM) when required to make the diagnosis with sufficient certainty. Immunohistochemical stains for macrophage markers (CD68 and CD163) were performed on some biopsies.

Kidney biopsies were processed according to standard procedures, including immunohistochemistry for immunoglobulins and complement, as well as ultrastructural investigation of McDowell fixed tissue.

2.3. Statistics and calculations

Statistical analyses were performed using IBM SPSS Statistics version 22. Continuous data are reported using the median (interquartile range [IQR]). To address the second objective, we used previously published data on the distribution of accumulated PVP in the body and data on the rate of elimination of PVP from the body.

3. Results

3.1. Patient characteristics

All 13 patients had a history of intravenous drug use, and all except one received opioid substitution therapy at the time of the first biopsy. The median age was 37 (range

Table 1 Biopsy site, year, and indication for the first biopsy showing PVP deposits for each case. Laboratory parameters are from the time of biopsy. Subsequent biopsies all showed PVP deposition.

ID	Biopsy site	Year	Indication	Hb (g/dL)	WBC (105/L)	TPC (109/L)	eGFR[a]	s−Creatinine (μmol/L)	Subsequent biopsies
1	Kidney	2009	Renal insufficiency	10.9	7.6	329	31	210	–
2	Kidney	2011	Renal insufficiency	10.2	6.7	226	21	275	–
3	Bone marrow	2011	Suspected malignancy	9.0	1.4	37	33	201	–
4[b]	Upper GI tract	2011	Anemia	7.8	5.3	142	54	133	UGI, B x 3, MB, BM, S
5	Kidney	2012	Renal insufficiency	12.6	5.0	241	23	277	–
6	Kidney	2012	Renal insufficiency	9.3	3.0	139	28	220	BM
7	Lower GI tract	2012	Diarrhea	11.4	5.3	224	29	217	BM, K, B
8	Clavicular bone	2012	Pathological bone fracture	9.6	5.6	336	38	172	BM
9	Kidney	2013	Renal insufficiency	11.5	6.5	316	30	170	GB
10	Bone marrow	2013	Suspected malignancy	11.0	4.0	260	24	260	UGI, LGI, LN, K
11	Kidney	2013	Renal insufficiency	11.3	7.6	272	40	168	M
12	Bone marrow	2013	Severe anemia	7.5	3.9	208	9	659	–
13	Skin	2013	Renal insufficiency and suspected PVP deposition	9.7	4.0	76	16	404	–
All patients			Median (IQR)	10.2 (2.2)	5.3 (2.6)	226 (154)	29 (14)	217 (105)	
Reference values				Hb	WBC	TPC		eGFR	s−Creatinine
			Male	13.4 − 17.0	3.5 − 11.0	145 − 348		≥90	60 − 105
			Female	11.7 − 15.3	3.5 − 11.0	145 − 348		≥90	45 − 90

Abbreviations: Hb, hemoglobin; WBC, white blood cell count; TPC, total platelet count; eGFR, estimated glomerular filtration rate; B, bone close to fracture; MB, maxillary bone; BM, bone marrow; S, skin; K, kidney; GB, gall bladder; UGI, upper gastrointestinal tract; LGI, lower gastrointestinal tract; LN, lymph node; M, skeletal muscle.

[a] eGFR (mL/min/1.73 m^2) calculated by the CKD-EPI formula.

[b] Laboratory parameters are from 2 years after the time of the first biopsy.

23−52) years, and 12 of 13 were male. All patients were seropositive for the hepatitis C virus. At the last follow-up in July 2020, six patients (46%) were deceased.

3.2. Clinical and laboratory findings

The main biopsy indications were renal insufficiency (recently discovered), pathological fractures, severe anemia, suspected malignancy, and abdominal complaints (Table 1). In addition, some patients had unspecific complaints, such as skeletal pain, reduced appetite, and weight loss. All patients had increased serum creatinine levels and hemoglobin levels below the reference level (Table 1).

3.3. Biopsy findings

A total of 31 biopsies from the 13 patients were reexamined, and PVP deposits were seen in all tissue samples. The deposits appeared as intracytoplasmic vacuoles in histiocytes. The vacuole content was stained light blue with H&E, red with Congo red stain, gray or black with PASM, and did not stain with Periodic acid−Schiff (PAS) (Fig. 1A−C). The vacuole content was not birefringent in Congo red or other stains. In the ultrastructural examination, vacuole content showed low-to-intermediate electron density with occasional electron-dense granules along the outer limiting membrane (Fig. 1D). Infiltrates of inflammatory cells other than CD 68−positive histiocytes were scarce. In biopsies from living patients, we observed PVP deposits in the kidney, bowel wall, bone marrow, jaws/periodontal tissue, lymph node, and skin.

In biopsies from hematopoietic bone marrow (n = 7), we observed PVP deposits in the marrow space. In four biopsies, the hematopoietic tissue was almost completely displaced by the PVP-containing histiocytes (Fig. 2A and B). In bone samples taken close to fracture sites (n = 5), the PVP deposits also affected necrotic bone tissue (Fig. 2C).

In kidney biopsies (N = 8), PVP deposits were mostly observed in the interstitium of areas affected by interstitial fibrosis and tubular atrophy (IFTA; Figs. 1B and 2D). IFTA was present in all biopsies and widespread in some, whereas glomerular abnormalities were scarce. Ultrastructural examination revealed vacuolated cells both in the interstitium and in the glomerular mesangium.

In samples from the upper and lower GI tract (n = 5), PVP deposits were found in the lamina propria and stretching down into the muscularis mucosae (Figs. 1C and 2E). The epithelial lining was unremarkable.

In a lymph node sample from a patient with lymphadenopathy, PVP deposits were widespread with little remaining lymphoid tissue (Fig. 1A).

Of two skin biopsies, one was performed because of a papular rash and revealed PVP deposits throughout the dermis (Fig. 2F). The second skin biopsy was from a person with renal insufficiency where a kidney biopsy was contraindicated. The biopsy was taken from healthy skin, and the finding of PVP deposits strengthened the suspicion of PVP deposition as the cause for the patients' renal insufficiency.

3.4. Autopsy findings

At the time of the last follow-up in July 2020, six patients were deceased. Two autopsies were available for reinvestigation. The first patient had chronic hepatitis C virus infection with a low viral load. He had a clinical course with months of diminished general health condition, muscle and skeletal pain, and severe weight loss. When admitted to the hospital, pancytopenia, kidney failure, elevated liver enzymes, and a suspected pathological process in the pancreas were uncovered. He deteriorated quickly and died at the end of prolonged hospitalization, presumably from multi-organ failure. The second patient was previously diagnosed with PVP deposition in biopsies from the GI tract, fractured bones, and bone marrow. He died 5 years after the diagnosis was established. During that time, he developed severe and chronic anemia, several pathological fractures, kidney failure, pancreatic failure, and severe cachexia [7].

The two autopsies showed largely similar macroscopic findings. Similarities included enlarged abdominal lymph nodes (Fig. 3A) and firm, white nodular lesions on the pelvic serosa, in the greater omental fold, and the mesentery. In both cases, the pancreas was hardened with a nodular cut surface (Fig. 3A). The pancreatic changes led to a constriction of the distal common bile duct with proximal distension (Fig. 3A). Microscopically, both autopsies revealed infiltrates of PVP-containing histiocytes in all tissue samples (description of each sampled tissue available in Supplementary material A). These included the lungs, heart, liver, pancreas, spleen, kidneys, adrenal glands, mesenteric tissue, lymph nodes, and bone marrow (Fig. 3B–G). The autopsy reports considered acute bronchopneumonia to be the immediate cause of death for the first patient and severe cachexia and multi-organ failure for the second patient. Both indicated widespread and extensive histiocytic infiltrates as part of the chain of events leading to death.

3.5. The source of the PVP deposits

We assessed the amount of PVP that had accumulated in two patients whose bone marrow biopsies appeared nearly full of PVP-containing histiocytes (Fig. 2A and B). To achieve this, we calculated a rough estimate of the total body PVP load based on literature data. Given an average bone marrow mass in male humans of 3000 g [8] and 0.005 g PVP per gram of PVP-saturated tissue [9], the entire bone marrow of these patients contained 15 g PVP. Given that the accumulated PVP in the bone marrow represents 6.5% of the total body load [2], the two patients had accumulated 230 g of PVP.

We then investigated whether injection of OSDs could have caused this level of accumulation of PVP. We studied two PVP-containing OSD preparations marketed in Norway at that time: a methadone syrup containing PVP K90 and buprenorphine tablets containing PVP K30 (information provided by the manufacturer). The calculation showed that patients would have had to inject 392 doses of the methadone syrup or 57,500 doses of buprenorphine

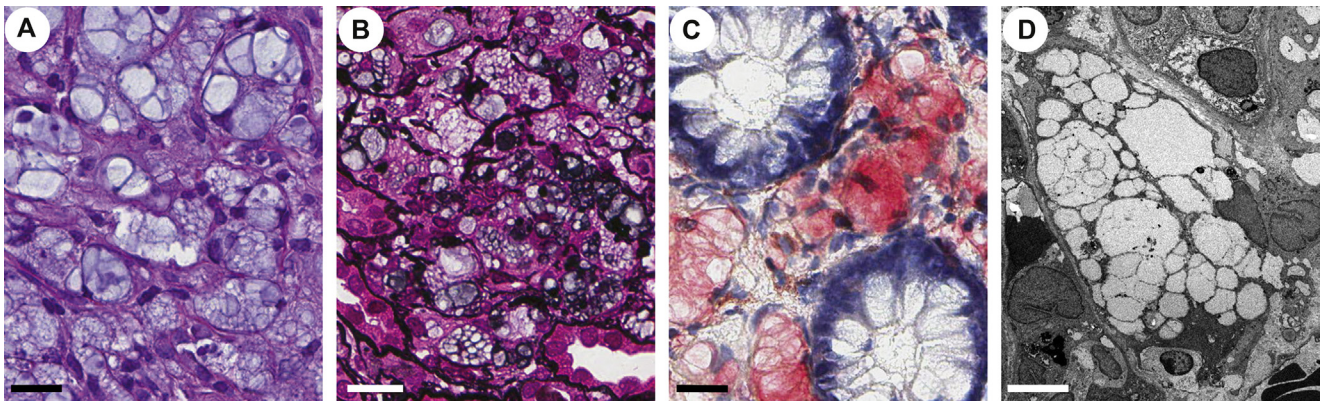

Fig. 1 Staining properties and ultrastructural appearance. (A) Lymph node biopsy. Section stained with PAS. Vacuole content does not stain with PAS and appears gray or light blue. (B) Kidney biopsy. Section stained with PASM. Vacuole content stains gray or black. (C) Biopsy from the lower GI tract. Section stained with Congo red stain. Vacuole content stains weakly to bright red. (D) Kidney biopsy. Ultrastructural investigation. Interstitial histiocyte extended by vacuoles with a low-to-intermediate electron-dense content. Tubular cells in the upper right corner. Scale bars: (A–C) 20 μm. (D) 5 μm. PAS, Periodic acid–Schiff; PASM, periodic acid silver methenamine; GI, gastrointestinal.

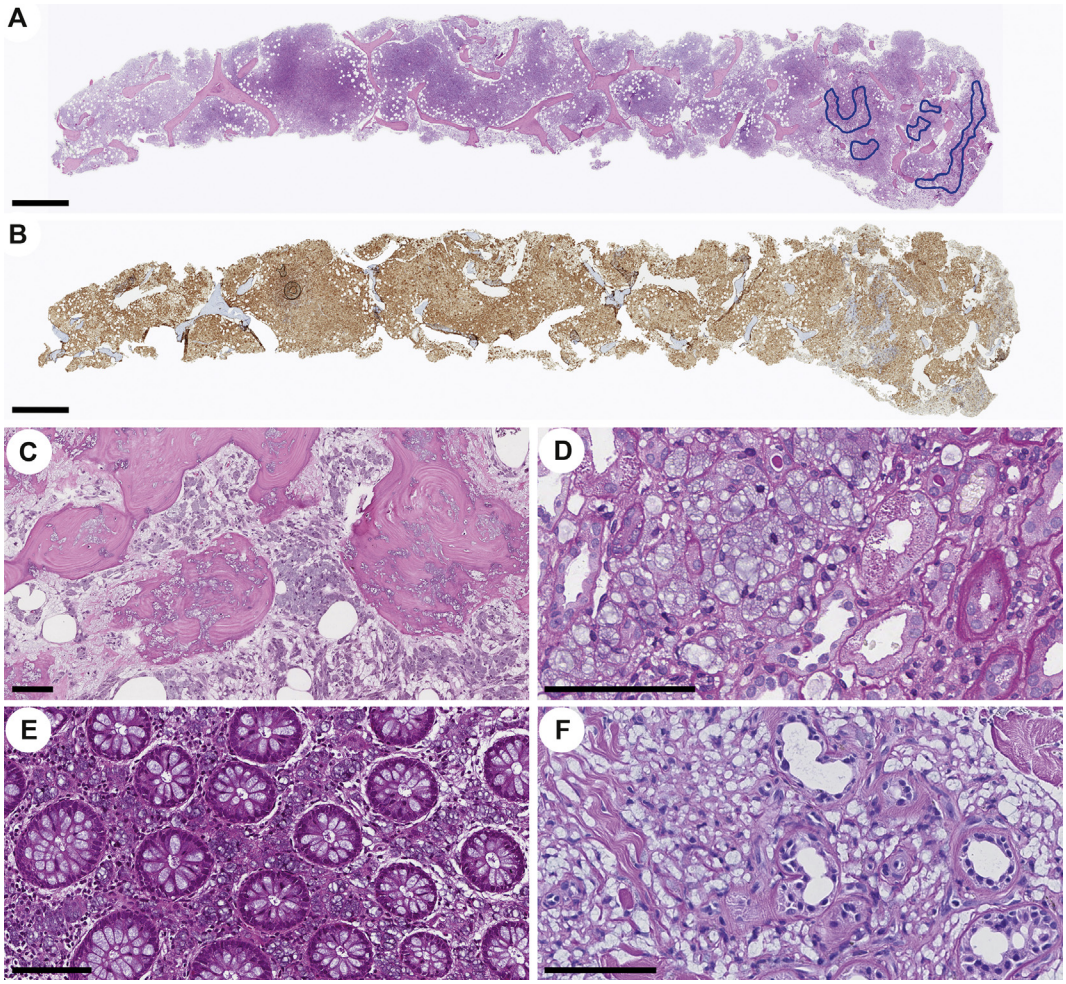

Fig. 2 Biopsy findings showing infiltrates of PVP-containing histiocytes. (A) Iliac crest, H&E: Marrow space is almost completely replaced by the infiltrates of histiocytes. The remaining hematopoietic tissue is annotated in blue. (B) Same biopsy as in Panel A, immunohistochemistry for CD68 (PGM1) illustrating the widespread infiltrates of histiocytes. (c) Bone from femoral head after hip replacement due to femoral head necrosis, H&E. Widespread histiocytic infiltrates in the marrow space. Necrotic bone with osteocytes only in singular lacunae and PVP deposits in many irregular spaces. (D) Kidney, PAS. PVP-containing histiocytes in the expanded interstitium. (E) Lower GI tract, H&E. Crypts surrounded by a slightly extended lamina propria with histiocyte infiltrates. (F) Skin, H&E. Adnexal glands in the deep dermis surrounded by infiltrates of histiocytes. Scale bars: A and B 1000 μm. C–F 100 μm.

tablets to obtain a total PVP body load of 230 g (detailed calculation available in Supplementary material B).

4. Discussion

This case series presents the findings from 31 biopsies and two autopsies from 13 patients with opioid addiction and PVP deposition. A methadone syrup containing large amounts of high MW PVP was the likely source of the bulk of accumulated PVP in these patients. Frequent indications for the biopsies were anemia, pathological fractures, gastrointestinal symptoms, and renal insufficiency. The main finding in most samples was extensive infiltrates of PVP-containing histiocytes, providing an explanation for the clinical symptoms. Of note, even a biopsy of healthy skin contained PVP deposits, which allowed a diagnosis when the intended target organ, the kidney, could not be biopsied. PVP deposition contributed to a fatal outcome in two patients whose autopsies showed PVP deposits in all microscopically investigated tissues.

4.1. The use of PVP in pharmaceuticals

PVP is widely used in the pharmaceutical industry as an excipient [1]. Its pharmacokinetic properties vary with its MW. Of special interest is that the body's ability to excrete PVP diminishes with increasing MW [2].

Low-to-moderate MW PVP was initially used as a colloidal plasma expander during the Second World War [3]. In the following years, there was emerging evidence that a portion of the administered PVP accumulated in the patients' tissues [2]. The observation of PVP accumulation resulted in the abandonment of PVP as a plasma expander in the late 1960s [10]. Meanwhile, the use of moderate-to-

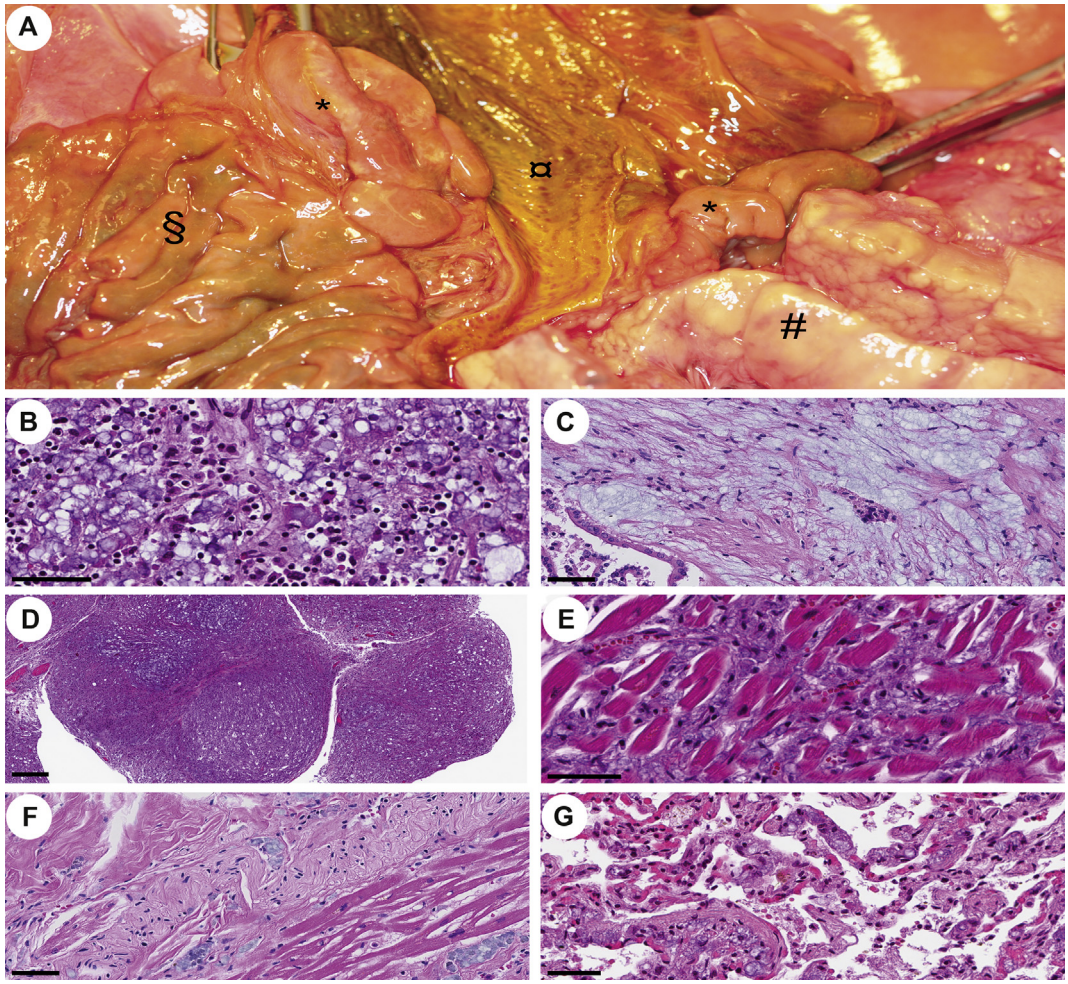

Fig. 3 Autopsy findings. Macroscopy (A) and H&E histology showing PVP-containing histiocytes (B–G). Panels A to F are representative of both autopsies. Findings depicted in Panel G were only seen in the first autopsy. (A) Upper abdominal preparation showing pancreas (#) with a nodular cut surface, constriction of the distal bile duct, and distension of the proximal bile duct (¤). Enlarged lymph nodes (*) on both sides of the bile duct. Duodenal mucosa (§) to the left. (B) Lymph node. Architecture disrupted by dense infiltrates of histiocytes. (C) Pancreas. Extensive fibrosis and infiltration by vacuolated histiocytes. Duct epithelium to the left. (D) Nodular lesion from the mesentery. The lesion is composed of PVP-containing histiocytes and fibrous tissue. (E) Myocardium. Vacuolated histiocytes between unremarkable cardiac myocytes and in areas of interstitial fibrosis. (F) Myocardium. Vacuolated histiocytes with peri- and intra-neural distribution. (G) Lung from the first autopsy. Vacuolated histiocytes in the alveolar walls. Scale bars: D: 300 μm. Otherwise, 50 μm.

high MW PVP as a retarding agent in preparations for daily parenteral administration continued until the late 1970s [3]. At that time, several cases of extensive and clinically relevant PVP deposition from such use of PVP had been reported [9,11]. The most recent reports of PVP deposition were Taiwanese cases resulting from frequent injections of PVP-containing preparations for "nutritional support" or as "blood tonics" [12–16]. The Taiwanese cases resulted in disease manifestations most comparable to the cases in our study.

4.2. Identifying PVP deposits

Recognizing PVP deposits is relatively straightforward, as PVP has distinctive staining properties. It does not stain with PAS, and it stains light blue with H&E, gray or black with PASM, and red with Congo red stain [9]. However, before 2013 when our department became aware that PVP deposition was occurring in patients with opioid addiction, deposits were not recognized at the time of biopsy. The diagnoses considered in the primary evaluation were various histiocytoses, mucin-containing histiocytes, or mucin-producing adenocarcinoma. The misdiagnosis of PVP deposition in the stomach as signet ring cell carcinoma has previously been reported [17]. Other forms of foreign materials may also be considered, as these are common findings in biopsies from patients with intravenous drug use [18]. Unlike many such materials, PVP is not birefringent [9]. Recently, there have been several reports of deposits of crospovidone (the nonsoluble version of

PVP) in tissue samples from persons who inject drugs [19,20]. PVP is easy to distinguish from crospovidone based on the differences in deposition sites and appearance. PVP deposits have been observed in almost all tissues of the body [21,22] and stain light blue in H&E. In contrast, crospovidone deposits are deeply blue, coral-like particles usually observed in the tissue around an injection site or in thromboemboli to the lungs. In addition, crospovidone deposits are often surrounded by a granulomatous reaction [19,20]. In conclusion, PVP deposits are easily identified if the observer is aware of this entity.

4.3. PVP deposition and disease

The biopsies in all our cases were performed because of disease symptoms, clinical findings, and laboratory abnormalities. The infiltrates of vacuolated histiocytes were considered the main finding in most of the biopsies and thus cannot be regarded as incidental. The spectrum of symptoms in our patients was in line with findings reported in the literature, the most common being anemia, pathological fractures, gastrointestinal symptoms, and renal insufficiency.

Anemia was present in all patients. In general, anemia is common among persons who inject drugs [23]. In addition, renal insufficiency, as seen in all our cases, increases the risk of developing anemia [24]. However, in four of the bone marrow biopsies, the PVP deposits almost completely displaced the hematopoietic tissue. Two reports from the 1990s presented similar findings in three patients with severe anemia who had received PVP-containing "blood tonics" [13,14]. The authors concluded, as we do, that the severe anemia was related to the extensive PVP deposits. On the other hand, we have no explanation for the combination of anemia with normal leukocyte and platelet counts in most of our patients.

Three patients suffered from pathological fractures due to osteonecrosis. These findings were in accordance with several previous cases that presented with bone destruction and pathological fractures attributed to PVP deposition [9,13–15]. The bone manifestations are similar to those seen in Gaucher's disease, another storage disease with histiocytosis and osteonecrosis as a major complication [25]. As for Gaucher's disease, hypoperfusion of osseous tissue due to extensive histiocytic infiltrates is one possible explanation for the occurrence of osteonecrosis in patients with PVP deposition.

Gastrointestinal tract biopsies were performed due to abdominal discomfort, vomiting, diarrhea, anemia, and/or severe weight loss. Biopsies revealed PVP deposits in the lamina propria, extending into the muscularis mucosae and the submucosa. Gastrointestinal PVP deposits have previously been described [21]. In another case, abdominal symptoms were attributed to mechanical obstruction by tumoral PVP masses in the mesentery [26]. It is uncertain whether PVP deposits in the bowel wall itself could cause bowel dysfunction and gastrointestinal symptoms. One possible mechanism could be disruption of bowel motility through the involvement of nerves in the bowel wall, as polyneuropathy caused by PVP deposits has been described [9]. Although we were unable to uncover the involvement of nerves in the gastrointestinal samples, we observed peri- and intra-neural distribution of PVP deposits in other organs. The autopsies revealed fibrosis and extensive PVP deposits in the pancreas, bile duct distension, and intra-abdominal tumoral PVP masses, which may have contributed to the symptoms experienced by some of our patients. However, abdominal complaints are common among persons with opioid addiction and are often related to the well-known side effects of opioids [27]. Hence, it was difficult to determine to what extent the gastrointestinal symptoms were related to the PVP deposits.

All patients showed impaired renal function, and kidney biopsies were frequent in our material. The main findings were similar in all biopsies: interstitial infiltrates of PVP-containing histiocytes and IFTA. Persons who inject drugs have an increased risk of developing renal insufficiency, and several mechanisms may lead to IFTA [28]. Because the findings in all biopsies were similar, and most of the changes commonly described in patients who inject drugs were not present [29], we consider PVP-containing histiocytes to be the most likely cause of atrophy and renal insufficiency. Notably, renal insufficiency has only rarely been reported in the setting of PVP deposition [30,31]. This discrepancy may be because of the extremely high MW of the deposited PVP in our cases.

4.4. Autopsies

Our material includes two autopsies. These are valuable, as they yield tissue samples from less accessible organs such as the heart, lungs, and pancreas. We found PVP deposition in all sampled organs. It is often a matter of discussion as to what extent and in which way an autopsy finding contributed to a patient's death. PVP deposits associated with the cardiac conduction systems, as observed in our cases, may induce arrhythmia. Widespread deposits in the parenchyma of the lungs may impair gas exchange. Edelmann et al. and Cabanne et al. described PVP deposition in the lung parenchyma [26,32], which is similar to the findings in one of our cases. The severe involvement of the pancreas in both our cases is puzzling. Kojima et al. observed pancreatic PVP deposits in 11 of 34 cases but did not emphasize this finding [22]. Except for focal acute inflammation in one of our cases, there were no morphological or clinical findings that could explain the widespread occurrence of pancreatic fibrosis. One of these patients had developed endocrine and

exocrine pancreatic insufficiency, which might have exacerbated the severe cachexia that contributed to his death.

There are two autopsy series from the 1960s that presented findings in patients who had received plasma substitutes containing low-to-moderate MW PVP [21,22]. PVP was not considered a causal factor for death except for one patient who died from acute liver failure after more than 2 months of daily plasma substitute infusions [22]. To the best of our knowledge, no other reports describe fatal outcomes from PVP deposition.

4.5. The source of the PVP deposits

A fundamental issue was to identify the source of the PVP deposits in the present cases. In recent years, PVP has mostly been used in oral and topical preparations [1]. Our patients shared similar backgrounds. First, all had a history of opioid addiction and intravenous drug use. Hence, the most likely cause for PVP deposition was the injection of opioids. Second, all except one of the 13 patients received opioid substitution therapy. Injection of OSDs is common among persons who inject drugs [4,5]. In fact, PVP was an excipient in three of the buprenorphine and one of the methadone preparations marketed in Norway [6]. Hence, these drugs were suspected sources. The buprenorphine preparations contained 8 mg of PVP K30 (MW 44−54 kDa) in a normal dose (information provided by the manufacturer). A common dose of the methadone preparation contained 585 mg of PVP K90 (MW 1000−1500 kDa), which was added as a thickener to prevent injection (information provided by the manufacturer). While much of the injected PVP K30 would be excreted within days, weeks, or months, the MW of PVP K90 does not allow renal filtration. Hence, the injected PVP K90 would probably remain in the body [2].

According to our calculations, the most severely affected patients had accumulated about 230 g of PVP. We estimated that it would take the injection of more than 57,500 common buprenorphine doses to reach this level of accumulated PVP, as opposed to less than 400 injections of a common dose of the methadone syrup. Furthermore, the first cases of PVP deposition were seen 2 years after the introduction of this specific methadone syrup to the Norwegian market in 2007. Taken together, it seems highly likely that the methadone preparation containing PVP K90 represented the predominant source of PVP in our cases. Based on the findings presented in this case series, this methadone preparation was withdrawn from the market in Norway and the European Union in 2014 [33]. There are still multiple potentially addictive prescription drugs on the market, which contain low-to-moderate MW PVP [34]. Frequent injection of such drugs may lead to some level of accumulation of PVP, but based on our calculations, we find it unlikely that this accumulation would be sufficient to cause disease.

4.6. Limitations

Chemical analysis can differentiate between PVP K30 and K90 but should be performed on fresh tissue. Unfortunately, we were unable to preserve usable fresh tissue from the autopsies or biopsies.

5. Conclusions

In Norway, persons who inject drugs developed PVP deposition with severe organ dysfunction from the injection of a methadone syrup containing high MW PVP. Our findings demonstrate the importance of documenting morphological changes and identifying foreign materials in tissue samples. Furthermore, pathologists ought to be attentive to signs of adverse effects from injection of oral drugs and should not hesitate to report such findings. Although the presumed source of PVP in these patients has now been withdrawn from the market, pathologists should be aware of PVP deposits when evaluating biopsies from this patient group. Finally, the pharmaceutical industry should bear in mind the risk of unintended parenteral use when designing drugs with addictive properties.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Code availability

Not applicable.

Authors' contribution

F.L. and I.V.S. made equal contributions to the article and are both considered as first authors. F.L. contributed to conceptualization, investigation, formal analysis, and writing the original article. I.V.S. contributed to investigation, formal analysis, writing the original article, and visualization. T.K.B. contributed to investigation, formal analysis, and reviewing and editing the article. C.O. and E.S. reviewed and edited the article. S.L. contributed to conceptualization, funding acquisition, reviewed and edited the article, and supervision.

Ethics approval

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK), reference number 27687.

Consent to participate

No new information or biological material was gathered on behalf of the study. Because of the social significance of the study, REK approved exemption from the consent requirement for the use of information and biological material from patients gathered in health care services. None of the included patients had registered in the Norwegian Registry of Withdrawal from Biological Research Consent.

Consent for publication

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2021.07.009.

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