Urine Cytology and Ethylene Glycol Poisoning

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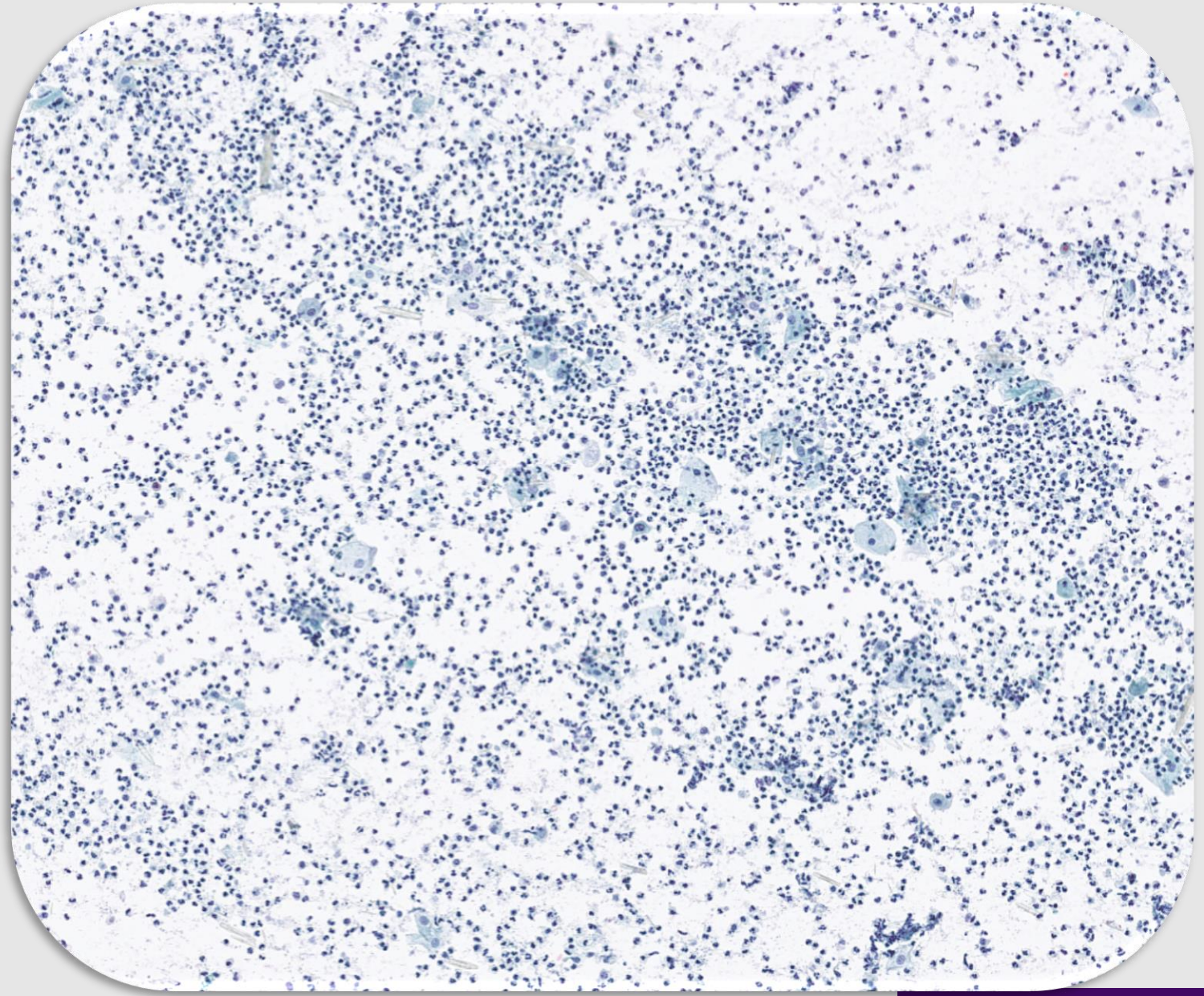
Clinical Information

- 57 year old woman admitted to A&E with reduced consciousness and aphasia.
- History of severe osteoarthritis, depression and previous mixed substance overdose.
- Blood tests show base excess of -15.5mmol/L and pH 7.16 Patient is acidotic.
- CT head showed no acute intra-cranial pathology.
- Suspected mixed substance overdose.

Clinical Information

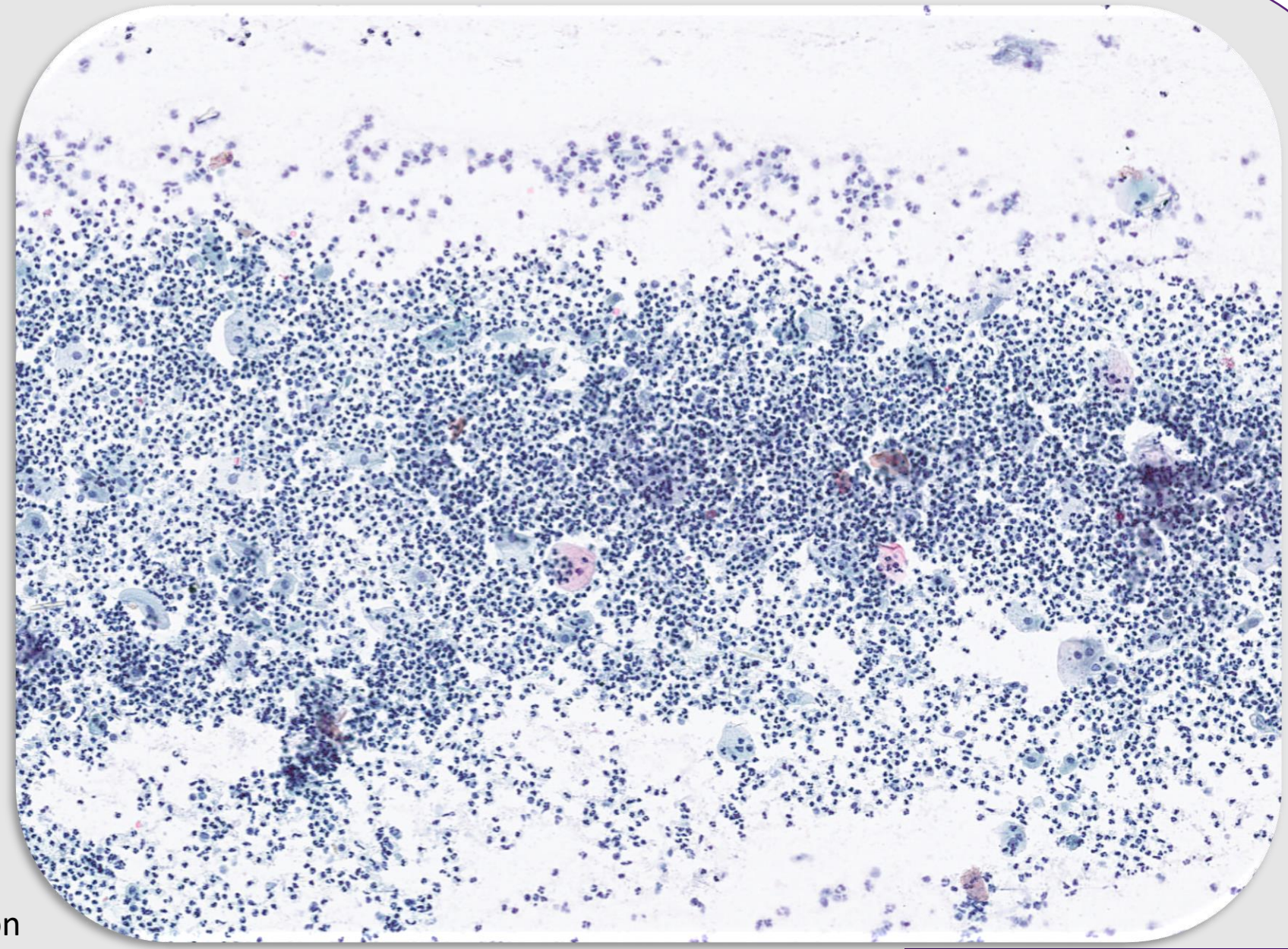
- Further blood tests show acute kidney injury with raised creatinine, sodium and urea. Urine output is significantly reduced.
- Toxicology results show no significant increase in paracetamol, salicylate or ethylene glycol.
- Clinically suspicious of ingestion of ethylene glycol despite no positive blood test results.
- Sample of catheter urine obtained for cytology and microbiology investigations. Request for presence of calcium oxalate crystals.

- A 20ml sample of cloudy, pale yellow urine is received in the laboratory.
- One cytospin slide is prepared and stained with Papanicolaou.



Pap
Magnification
X10

- The sample contains numerous neutrophils admixed with benign squamous cells and urothelial cells.
- No atypia or features of malignancy are seen.



Pap
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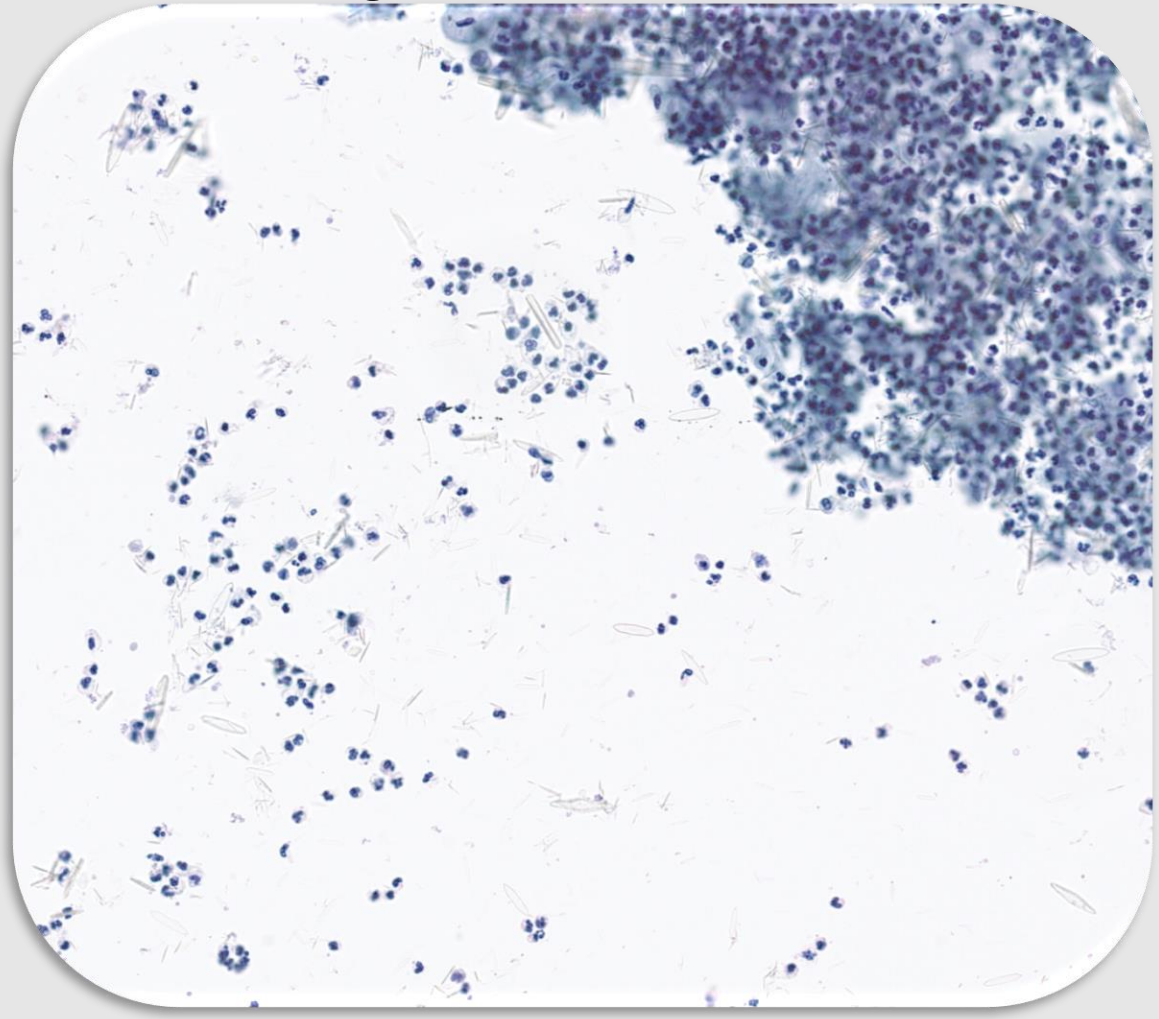
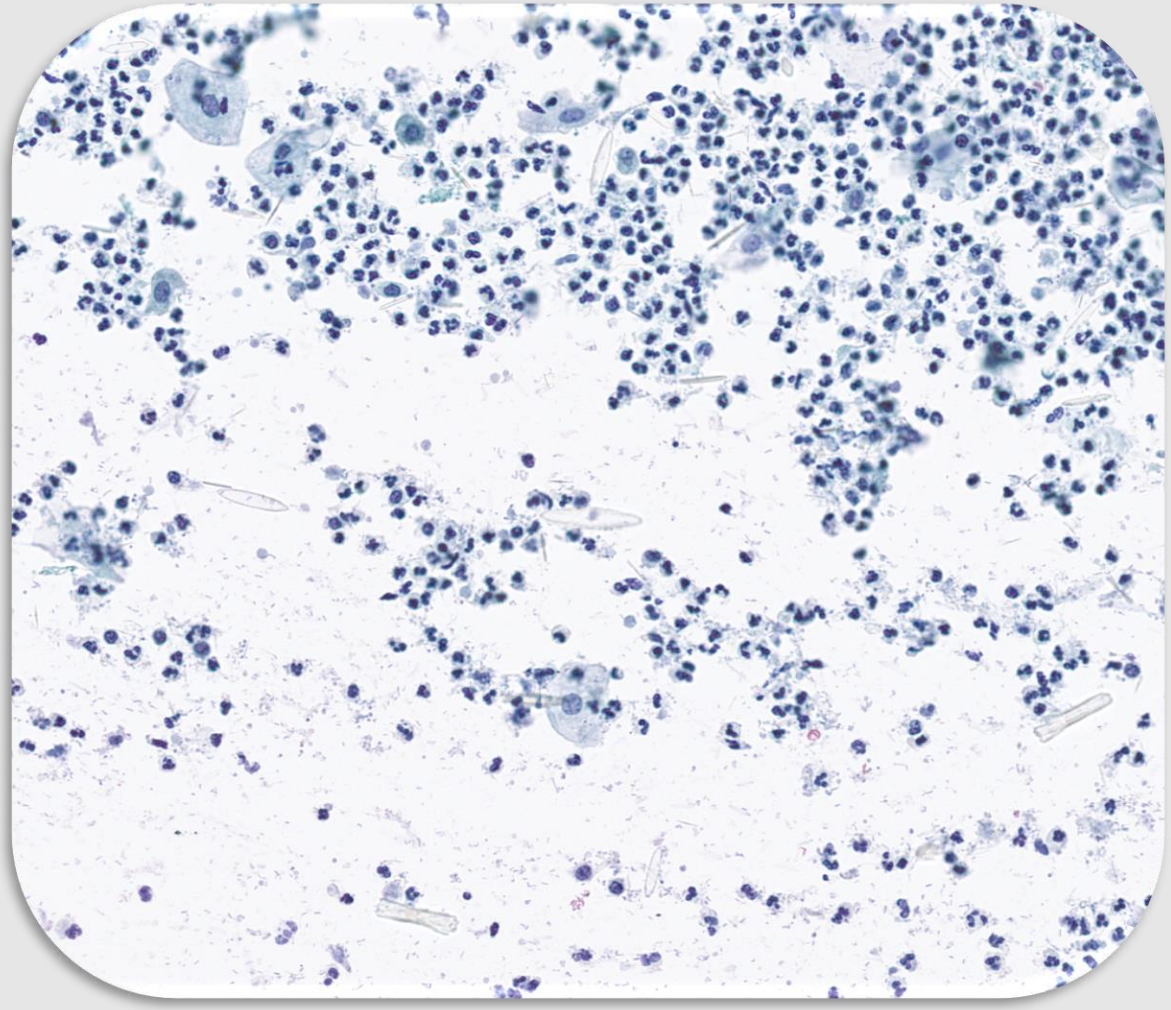
- At higher magnification unstained crystals can be seen in the background and amongst the cellular material.

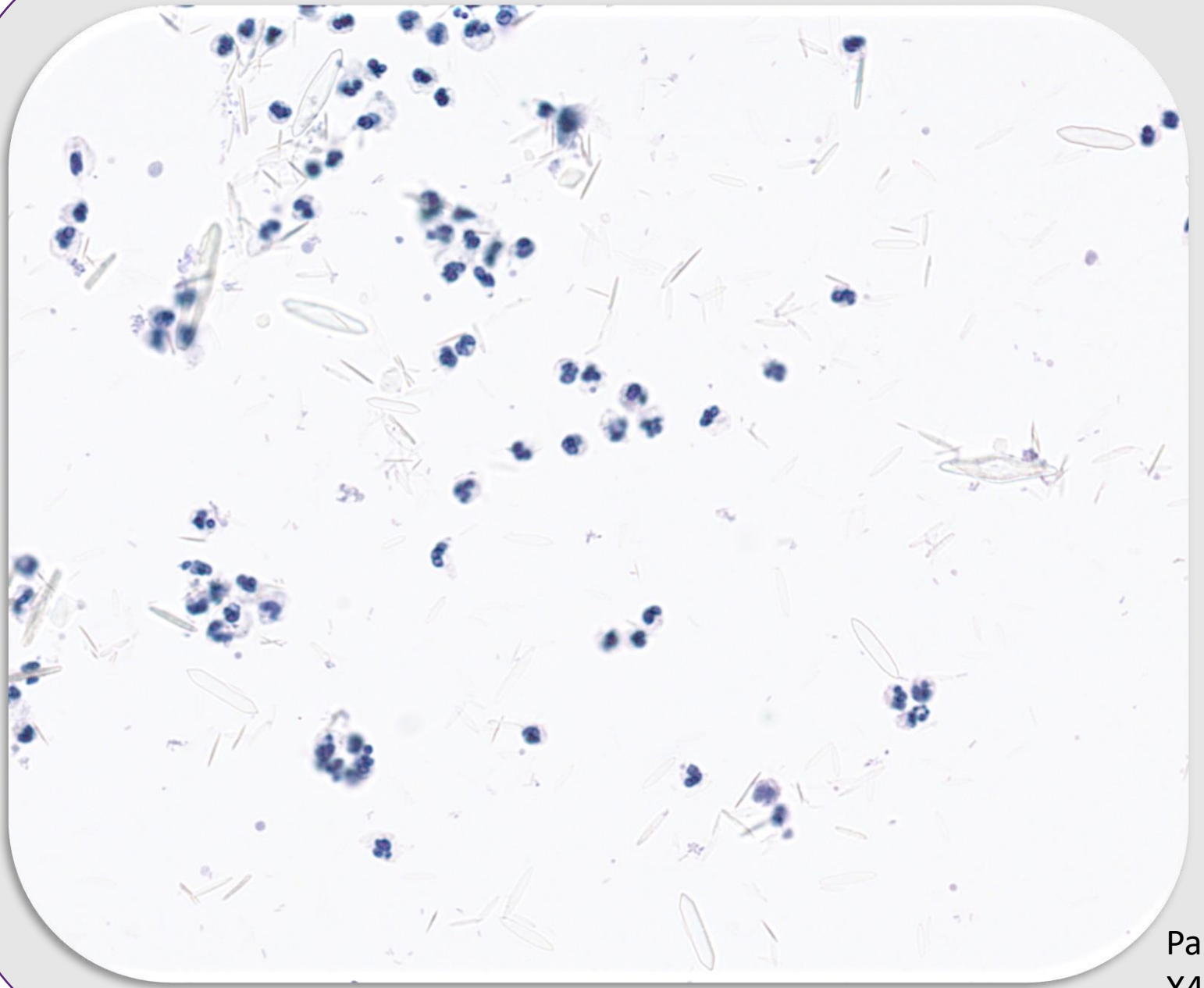


Pap Magnification X15



Pap Magnification X20

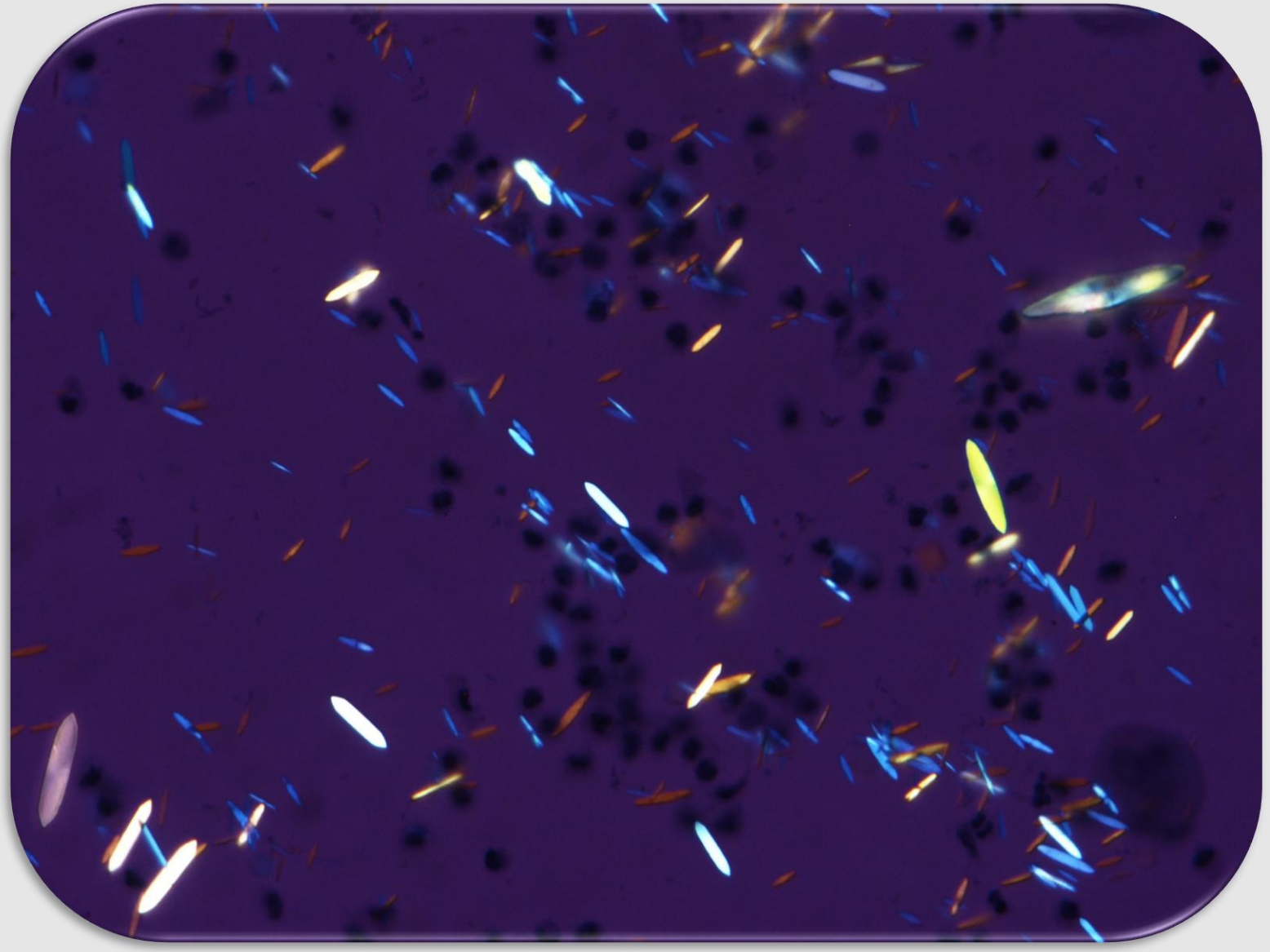
BAC British Association for Cytopathology



- Morphology of the crystals shows some variation. Needles, ellipse/cigar, rectangles and blunt ended polyhedron forms are seen. Some of the crystals are similar shapes to hippuric acid, but have a blunt end rather than a point.
- These are suggestive of calcium oxalate monohydrate crystals[(1)].
- Appearances differ from the more commonly seen envelope shaped crystals of the dihydrate form of calcium oxalate.

Pap Magnification
X40

- Under polarising microscopy the crystals can be seen more clearly and exhibit positive birefringence.



Pap Magnification X40, polarising filters with red compensation

Diagnosis

In the context of the clinical details of ingestion of ethylene glycol, the morphology is consistent with calcium oxalate monohydrate crystals.

Key Factors

- Clinically, decreased urine production, low blood pH, metabolic acidosis. Hypocalcaemia and hyperkalemia.

- Presence of calcium oxalate monohydrate (COM) crystals can support the clinical suspicion of ethylene glycol poisoning. Initial blood tests for ethylene glycol may not show increased levels as the substance is rapidly metabolised.

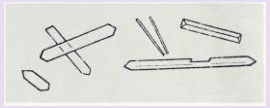
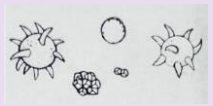
- Ethylene glycol is metabolised by alcohol dehydrogenase in the liver causing generation of a sequence of products including oxalic acid and glycolic acid. Oxalic acid can bind with calcium and deposition of the resultant COM crystals causes tissue damage, especially in the kidneys[1,2].

Common urinary crystals

- Crystals are often seen in urine cytology, but are usually of little clinical significance.
- Crystal deposition can be linked to diet. Increased consumption of some foods can cause an increase in crystals e.g. rhubarb and calcium oxalate (dihydrate).
- A urine specimen may contain both calcium dihydrate and calcium monohydrate forms[(3)].
- Clinical context is key and, in this case, the suspected ingestion of ethylene glycol supported the reporting of crystals present.

Common urinary crystals

Examples of common crystals are seen in the table below [3,4].

Crystal type	Appearance		Significance
Calcium oxalate dihydrate		Envelope, colourless, octahedral	Associated with calculi and diet
Calcium oxalate monohydrate		Ovoid (picket fence), dumbbell, hourglass shapes, colourless	Can be seen in ethylene glycol poisoning
Uric acid		Yellow brown, oval to rhomboid shapes	Low urinary pH. Can be seen in diabetes, metabolic syndrome, chemotherapy treatment
Triple phosphate (struvite)		Coffin lid shaped prisms	Urinary tract infections with alkaline pH e.g. Proteus
Hippuric acid		Rectangle with pointed ends	Associated with diet
Ammonium urate (thorn apple)		Round or spherical with points	Associated with ammoniacal fermentation and sample degeneration

Treatment

- Initial treatment is administering sodium bicarbonate to counteract metabolic acidosis.
- Subsequent treatment involves neutralising the toxic products of ethylene glycol and inhibition of alcohol dehydrogenase.
- Traditionally this is achieved by administering high doses of ethanol, intravenously or orally. Disadvantages of this technique include variable metabolism rate of alcohol, symptoms of intoxication (difficult to differentiate from presenting symptoms) and a requirement for close monitoring of treatment[(5)].
- An alternative approach is use of the drug fomepizole which has been proven to inhibit alcohol dehydrogenase but without the disadvantages of ethanol treatment[(6)].
- Subsequent haemodialysis may be required.

References

1. Koda, R Watanabe, H and Iino, N. Calcium oxalate monohydrate crystals in ethylene glycol poisoning. Clin Exp Nephrol. 2017 21:741-742

2. Sheta, HM, Al-Najami, I Christensen, HD and Madsen, JS. Rapid Diagnosis of Ethylene Glycol Poisoning by Urine Microscopy. Am Journal of Case Rep. 2018 19:689-693

3. Torous VF, Dodd LG, McIntire PJ and Jiang XS. Crystals and crystalloids in cytopathology: Incidence and importance. Cancer Cytopathology. 2022 130;10:749-832

4. Lee A-J, Yoo E-H, Bae Y-C et al. Differential identification of urine crystals with morphological characteristics and solubility test. J Clin Lab Anal. 2022; 36(11)

5. Scalley RD, Ferguson DR, Piccaro JC, et al. Treatment of Ethylene Glycol Poisoning. Am Fam Physician 2002; 66(5):806-813

6. Brent J, McMartin K, Phillips S, et al. Fomepizole for the Treament of Ethylene Glycol Poisoning. N Engl J Med 1999 340:832-838