Original article

Consultation between forensic and clinical pathologists for histopathology examination after forensic autopsy

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Abstract

The magnitude of the diagnostic benefit conferred by performing histopathological examinations after medico-legal/forensic autopsies remains debatable. We have tried to address this issue by reviewing a series of histopathology referrals concerning medico-legal autopsies in real-world routine practice. We present an audit of the consultations provided to forensics by clinical pathologists at our institute between 2015 and 2018. Over this period, 493 post-mortem examinations were performed by forensic pathologists. Of these cases, 52 (11%) were referred for histopathology. Gross assessment was requested in 22/52 (42%) cases. Histopathology examination was performed on single organs in 15/52 (29%) cases, primarily on the lung and heart, whereas parenchymatous multi-organ analysis was carried out in 14/52 (27%) cases. Bone-marrow sampling was studied in 4/52 (8%) cases. Immunohistochemistry was needed in 16/52 (31%) cases, special stains in 9/52 (21%) cases and molecular analysis in 4/52 (8%) cases. Focusing on technical processes, standard methodology on pre-analytical procedures was changed in 10/52 (19%) cases in order to answer specific diagnostic questions. We showed that although most of the time the diagnosis is clear by the end of dissection on the basis of the macroscopic findings, histopathology can provide, modify or confirm the cause of death in many medico-legal/forensic cases. Therefore, it is desirable that forensic pathologists and clinical pathologists establish robust working relationships in a cooperative environment. We conclude that it is important to implement guidelines based on real-world routine practice in order to identify cases where histopathology can provide useful contributions, which in our experience applied to 11% of forensic cases.

Keywords

Autopsy, histopathology, consultation, forensics, pathologists

Introduction

Medico-legal/forensic and clinical autopsies usually differ in their purpose and histopathological requirements. Forensic autopsies are performed by forensic pathologists to determine the cause and manner of death and

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to document traumatic lesions in order to provide information to family members and investigative agencies or to testify in court. Clinical autopsies are carried out by general pathologists to diagnose clinically occult diseases, potentially infectious diseases and neoplastic diseases and to provide information to families about potentially inheritable diseases. Although medico-legal autopsies often include histopathological analysis, this does not occur as often as it does in clinical autopsies.[1]

Overall, the benefit of histopathological examinations during medico-legal and forensic autopsies remains debatable. De La Grandmaison et al. maintain that histology of the main organs should be carried out systematically in routine forensic autopsies,[2] whereas Molina et al. state that such a routine practice is not always necessary.[1] In order to address the dilemma posed by this debate scientifically, we audited specific cases in which referrals were made to our histopathology department by forensic pathologists for examination of relevant tissues or organs.

Methods

Ethics statement

This study was approved by the Institutional Internal Review Board of the University of Verona in compliance with the seventh revision (2013) of the Helsinki Declaration of 1975. All data and images were anonymised.

Data collection

Over the 4-year period between 2015 and 2018, 493 subjects underwent full post-mortem examination by forensic pathologists at the Institute of Legal Medicine (University of Verona). All the histopathological referrals were made by the general pathologists of the pathology unit where the procedures were performed. Data from the referrals were collected from the pathology unit and legal medicine archives.

All gross and histopathological findings were reviewed, while special stains and immunohistochemical and molecular analyses were recorded, and a comparison between the technical standards (pre-analytical processes) for the different cases was made. All data and personal references were suitably anonymised. Overall, the study approval was first discussed thoroughly and then promoted.

Results

Fifty-two histopathological referrals were made by clinical pathologists from a series of 493 medico-legal/forensic autopsies, with a referral rate of 11% (Table 1).

Table 1. Consultation interface between medico-legal forensic and surgical pathologists: 52/493 (11%) forensic autopsies deserved consultation interface with surgical pathologists (Verona Audit 2015–2018.)

Methodology	*n*	%	
Gross analysis	*22*	*42%*	
Primary sampling	10	19%	Appropriate standard of gross sampling, appropriate time of fixation, slicing of fresh organs
Secondary sampling	12	23%	Organ re-sampling in the gross room due to underestimated primary gross sampling
Histopathological analysis	*31*	*60%*	
Single organ	15	29%	90% lung or heart
Multi-organ	14	27%	Lung, heart, kidneys, liver, spleen, brain, bowel, thyroid, adrenal glands, stomach, bladder
Bone marrow	2	6%	From the sternum
Immunohistochemical analysis	*16*	*31%*	Most pulmonary nodules; other i.e. confirming mesothelioma, adrenal neoplasia, pancreatic mass
Oncological typing	10	19%	i.e. infiltration of bone-marrow suspicious for neoplasia, hepatic/pulmonary nodules
Non-oncological diagnosis	6	12%	i.e. characterisation of inflammatory tissues (i.e. myocarditis, meningitis, reactive processes)
Special stain analysis	*9*	*17%*	Alcian–PAS in lung for diagnosis of DAD Masson's trichrome staining for ischaemic area and for arytmogenic dysplasia/adipositas cordis Grocott, Gram- and Elastic fibre staining protocol
Molecular analysis	*4*	*8%*	FISH analysis for material exchange (when exchange is related to female/male patients); ALK
Modified protocols	*10*	*19%*	30 μm tissue section for asbestos fibres, Oil Red O from formalin tissue, gross re-sampling

PAS: periodic acid–Schiff; DAD: diffuse alveolar damage; FISH: fluorescent in situ hybridisation; ALK: anaplastic lymphoma kinase.

The procedures and the results of these consultations are summarised in Figures 1–8.

Gross assessment was requested in 22/52 (42%) cases. In 10/22 (45%) cases, the general pathologist cooperated with the forensic pathologist in the autopsy room, providing direct support with regard to the interpretation of the macroscopic findings. In the remaining 12 (55%) cases, referrals were made only at a later date after completion of the autopsy. This resulted in a second gross examination with tissue sampling in addition to what was taken during the initial autopsy.

Histopathological examination was performed on single organs in 15/52 (29%) cases, primarily on the lung and heart, whereas systematic multi-organ histopathology was performed in 14/52 (27%) cases. Bone-marrow sampling was studied in only 2/52 (4%) cases, while immunohistochemistry (IHC) was required in 16/52 (31%) cases, special stains in 9/52 (21%) cases and molecular analysis in 4/52 (8%) cases.

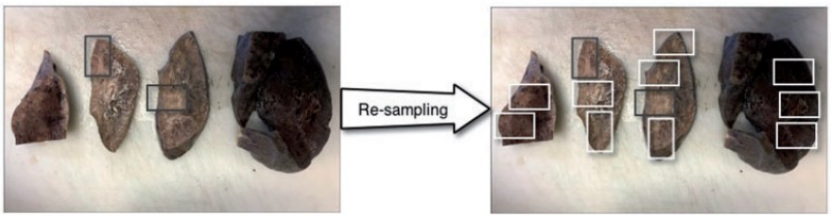

Figure 1. Gross interface. A case from a lung: evaluation of primary samples was not sufficient to discriminate between the two differential diagnoses (i.e. DAD or interstitial pneumonia). After gross re-sampling, a final diagnosis of DAD was made after doubling paraffin blocks (dark square vs. white square). DAD: diffuse alveolar damage.

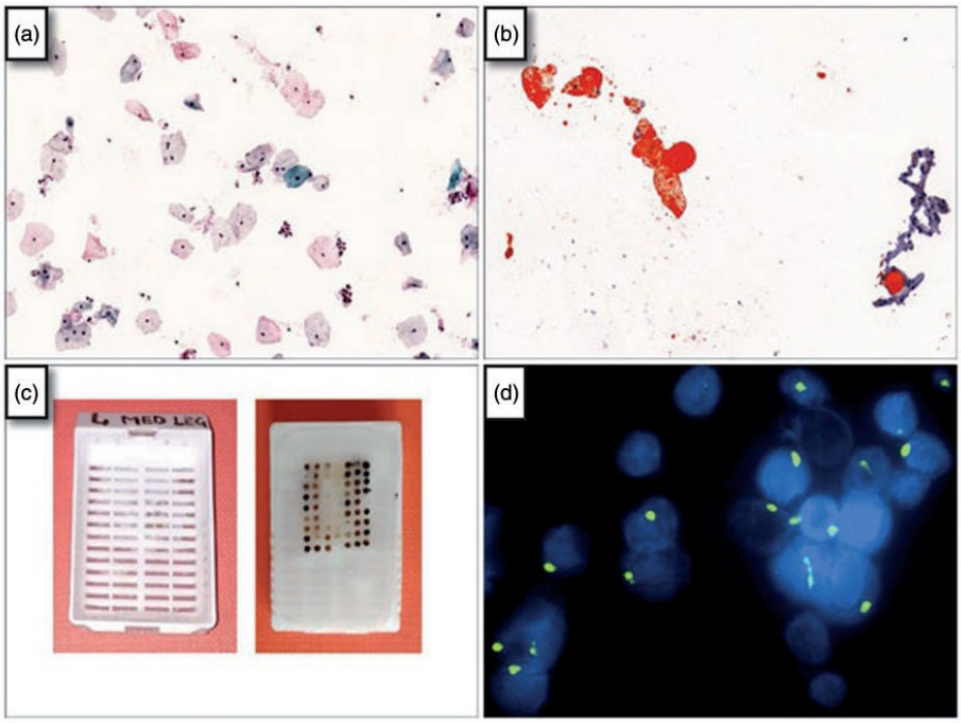

Figure 2. Interface for cyto-histopathology and niche methodologies. (a) Cytological smear to rule out cervical dyskaryosis/dysplasia and human papillomavirus cytopathic effect. (b) Oil Red O staining after washing a tissue sample from pulmonary formalin-fixed sample for 48 hours, showing appropriate adipose globules entrapped within parenchyma (right) and false-positive deposition on the left. (c) Punch (0.6 mm) biopsies per tissue core to build multi-spot of tissue available for wider multi-profiling (i.e. post-mortem interval analysis) or research. (d) Molecular fluorescent in situ hybridisation analysis, with the presence of the single fluorescent Y chromosome centromeric probe on 4,6-diamidino-2-phenylindole-stained nuclei showing the male tissue (exchange of tissue material in the lab between female and male cases).

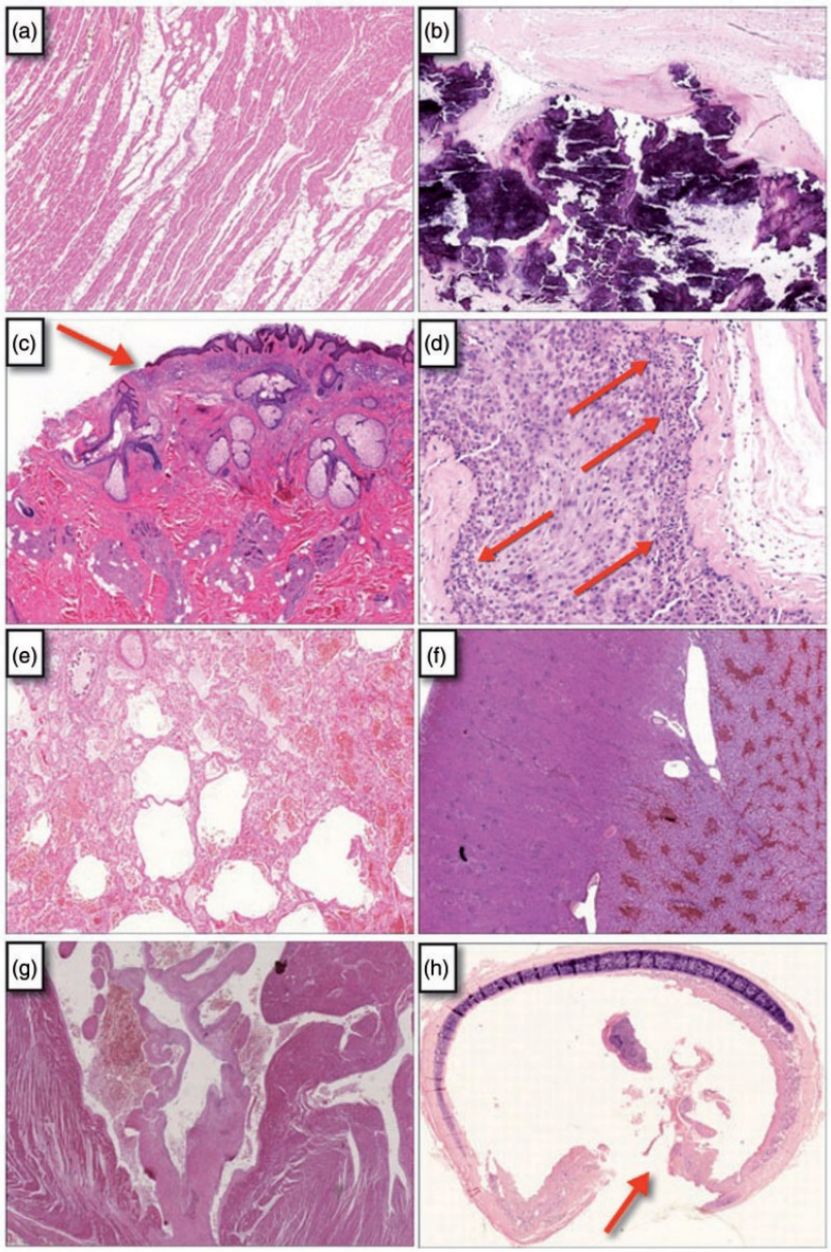

Figure 3. Histopathological interface with additional staining needed. (a) Presence of adipose tissue in between fibromuscular fibres in the heart (adipositas cordis vs. arrythmogenic dysplasia, trichrome staining). (b) Presence of coronary atherosclerosis and calcification with estimation of the coronary occlusion (CD68). (c) Skin with rupture of the continuity of the epidermis; vitality of the tissue (death before or after accident, boat propeller wound). (d) Presence and grading of chorioamnionitis (CD15). (e) Lung parenchyma with non-specific morphological details (new macroscopic sampling and special stains were required; PAS, trichrome, Grocott, CD20 and CD3). (f) Renal parenchyma with blood stasis in the medulla (traumatic surgical lesion; CK8-18). (g) Heart in a newborn with fibrolamellar tissue proliferation in the ventricular cavity (fibroelastosis vs. none; elastic fibres staining was required needed). (h) Suspected intubation damage (laryngotracheal ring) (CK8-18, CD3 and CD68). PAS: periodic acid–Schiff.

Most of the IHC analyses (75%) were made to rule out a neoplastic process or for histological typing of tumours (i.e. pancreatic lesions vs. adenocarcinoma: one case; confirmation of mesothelioma: five cases; atypical infiltration of bone marrow suspected of containing neoplasia: two cases; adrenal-gland neoplasia: one case; benign solid-cystic hepatic nodules vs. cholangiocarcinoma: one case; Table 1). In the remaining cases, analysis was required to characterise inflammatory tissues (and to rule out lymphoproliferative diseases) primarily by using CD20, CD3, CD68 and CD15 antibody panels on the brain (meningitis vs.

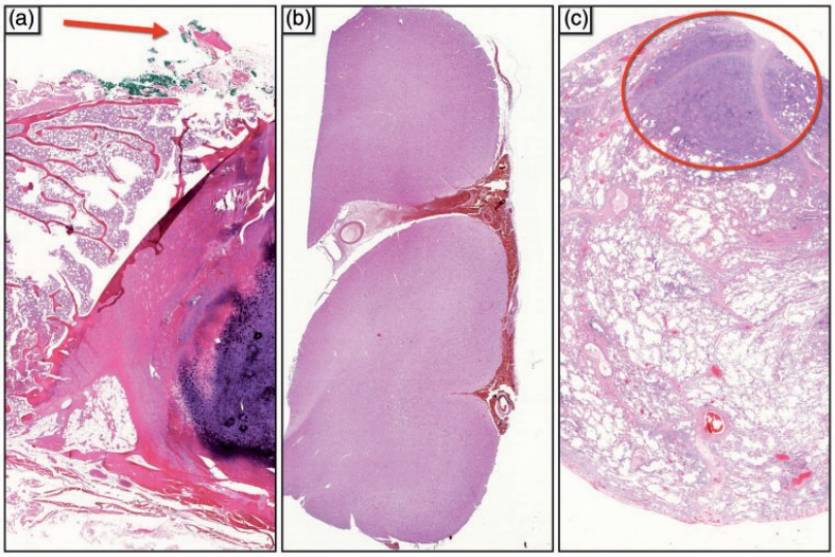

Figure 4. Histopathological interface. (a) Sternum: damage of cortical lamellar bone due to sternal puncture. (b) Accident brain trauma (presence of subdural haemorrhage). (c) Neoplastic nodule in lung parenchyma.

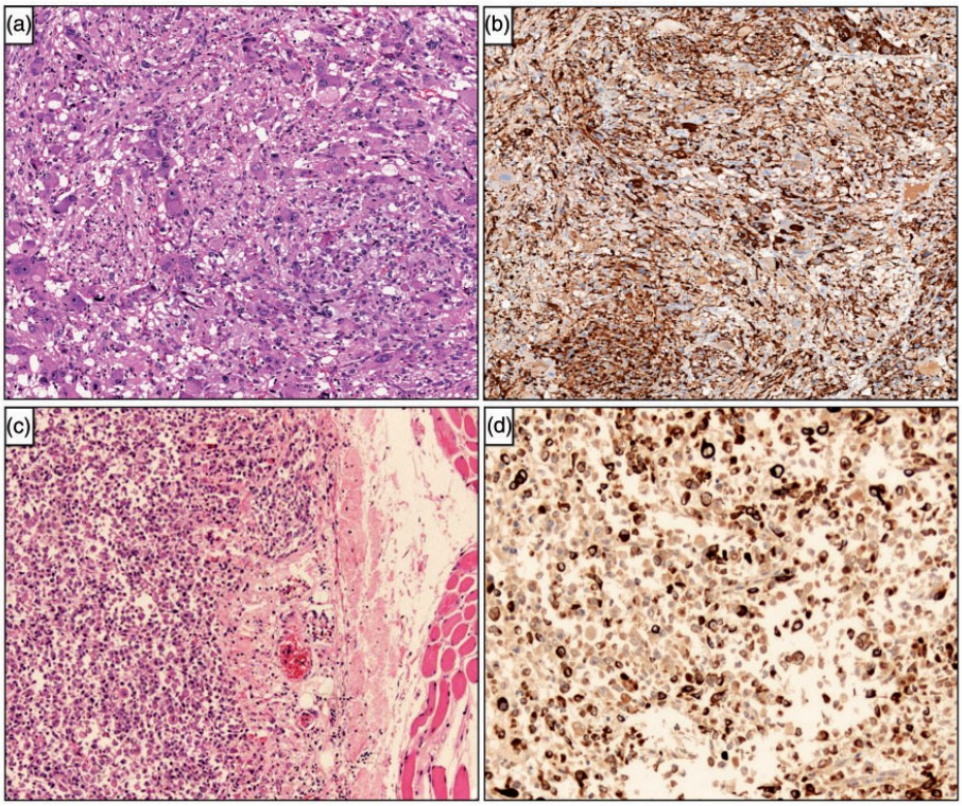

Figure 5. Immunophenotypical interface analysis. (a) An example of adrenal neoplastic nodule with (b) chromogranin diffuse expression. (c) An example of pleuropulmonary mass showing (d) diffuse calretinin expression.

reactive infiltration of inflammatory cells post trauma: one case), heart (myocarditis: four cases) and colon (in view of pre-existing chronic bowel inflammatory disease: one case).

The most commonly used special stains (>90% of requests) were periodic acid–Schiff (PAS) and Alcian–PAS (on lung tissue for diffuse alveolar damage), Grocott (on lung tissue to rule out fungal infection)

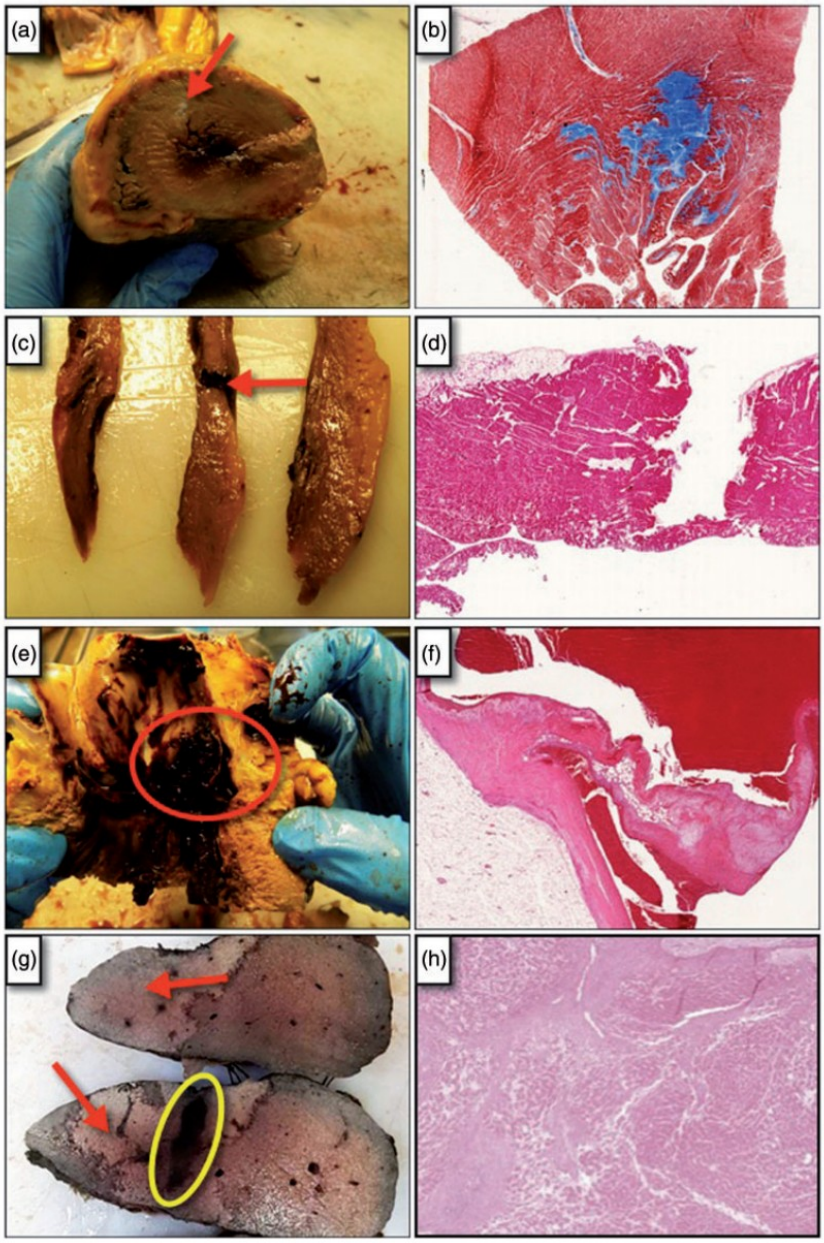

Figure 6. Gross review. Heart macroscopic evaluation showing a small whitish area (a) in the left ventricular cavity, positive for PAS special stain (b), showing a fibrosclerotic area due to old ischaemic process; heart damage due to sternal punctate ((c) and (d)); dissection of the aortic vessel with haemorrhage and elastic lamellar disruption ((e) and (f)); liver with damage from a transbronchial probe during lung biopsy: dark haemorrhage tract and adjacent liver injury ((g) and (h)).

and Masson's trichrome stain (on heart and lung tissue). Molecular analysis by fluorescent in situ hybridisation (FISH) was performed in three cases to test for the presence of tumour-specific gene rearrangements and oncological biomarkers like anaplastic lymphoma kinase (ALK) gene, Ewing sarcoma breakpoint region 1 (*EWRS1*) gene and chromosome 1p/19q co-deletion; it was performed also to verify an exchange of tissue between two consecutive female and male patients by using the X/Y chromosome probes (one case). Sections with increased tissue thickness (5–7 μm vs. 3–5 μm) were required to perform the molecular FISH analysis in order to verify the exchange of material between the two consecutive female and male patients.

Focusing on technical processes, in order to answer critical forensic questions, the standard methodology for pre-analytical procedures was changed in 10/52

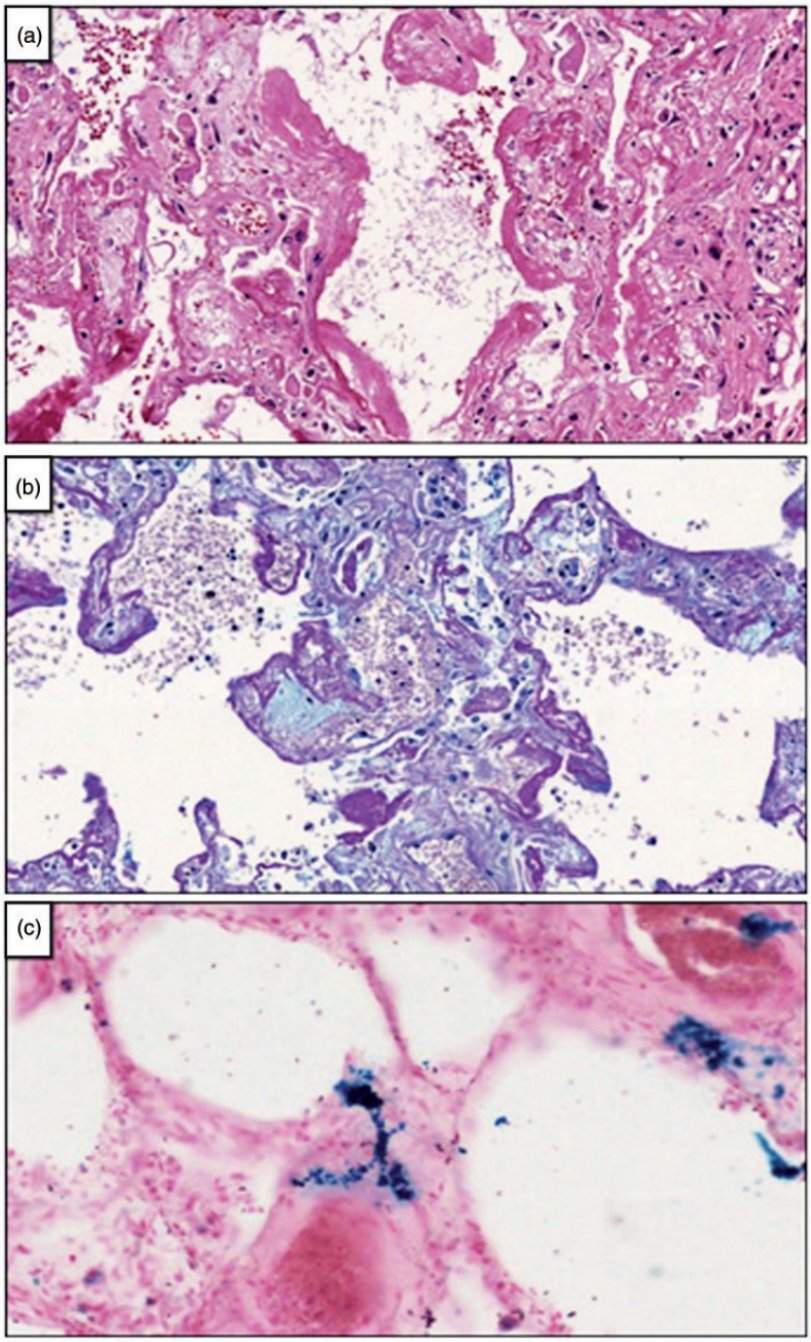

Figure 7. Interface for special stains or modification of standard routine protocols. Pulmonary parenchyma with the presence of intra-alveolar deposits, suspected hyaline membranes (a) positive with PAS staining (b); asbestos fibres research on lung tissue with Perls' staining: new 30 μm tissue sections were required (avoiding standard 3–5 μm tissue sections) to enhance sensitivity of the technique (avoiding false-negative analysis).

(19%) cases. Namely, Perls' special stain for asbestos fibres required re-sampling/new tissue sections of pulmonary parenchyma because of the need for 30 μm thick sections of lung tissue (four cases). Oil Red O stain was performed after daily (24 hours) washing under running water in order to remove formalin from lung tissue which had been fixed for up to 48–72 hours (four cases). These changes were made to avoid potential false-negative results during interpretation. Bone marrow (from the sternum) had to be reassessed in two (4%) cases because of inadequate fixation of the samples. The second sternal samples were

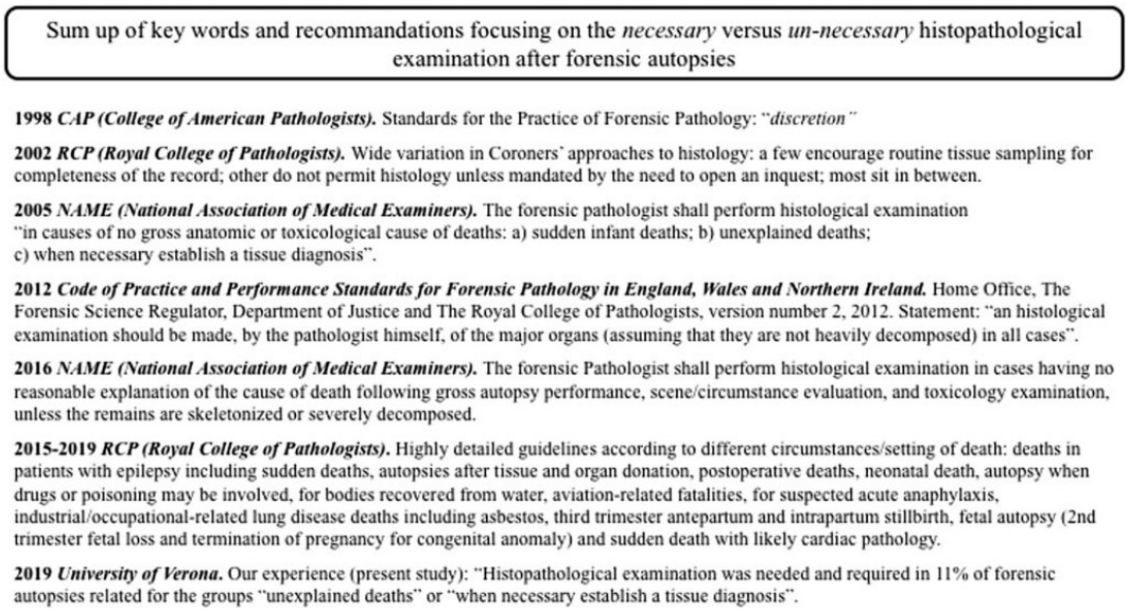

Figure 8. Summary of recommendations and statements regarding histopathological evaluation in forensic autopsies.

obtained with a new sectioning method, using slow daily decalcification with control of potential tissue sectioning. In the remaining cases, we had no opportunity to obtain new sections from the sternum due to the lack of suitable bone samples (four cases).

A subset of forensic referrals to the clinical pathologists required a combination of analyses (55%). This included macroscopic and histopathological examination with special stains or immunostaining procedures or even molecular investigations. Among these, it is worth highlighting a case in which extra tissue from the lung was taken in order to obtain several more paraffin blocks for PAS stains to differentiate between diffuse alveolar damage and interstitial pneumonia (Figure 1).

Other significant investigations included: a cytological smear to rule out the presence of cervical dyskaryosis (dysplasia) and/or human papillomavirus cytopathic effect (one case); Oil Red O staining after washing formalin-fixed lung tissue samples for 48 hours, showing appropriate adipose globules (two cases); punching 0.6 mm tissue cores to build tissue microarray paraffin blocks for post-mortem immunophenotypical interval post-mortem analysis; researching the single fluorescent Y chromosome by using a centromeric molecular DNA probe and 4,6-diamidino-2-phenylindole stains, showing nuclei with a single male fluorescent Y body spot to verify the exchange of tissue samples (two consecutive cases, respectively female and male; two cases; Figure 2); researching the presence of adipose tissue between fibromuscular myocardial fibres in the heart (adipositas cordis vs. arrhythmogenic dysplasia) using trichrome staining; the presence of coronary atherosclerosis and calcification with estimation of a coronary occlusion and CD68 immunostaining (two cases); analysis of tissue vitality in a skin sample from a boat propeller wound in order to determine if death occurred before or after the collision (one case); researching the presence and grading of chorioamnionitis with additional CD15 immunostaining (one case); new macroscopic sampling and multiple special stains (PAS, trichrome, Grocott, CD20 and CD3) to study lung parenchyma with non-specific morphological findings (two cases); evaluation of a traumatic surgical lesion of the renal parenchyma with blood stasis in the medulla by CK8-18 (one case); elastic fibres staining to identify cardiac fibroelastosis in a newborn with fibrolamellar tissue proliferation in the ventricular cavity (one case); demonstration of suspected intubation-related damage of the laryngotracheal ring by CK8-18, CD3 and CD68 (one case; Figure 3); researching sternal damage of cortical lamellar bone following sternal puncture (one case); identification of subdural haemorrhage related to brain trauma (one case); analysis of a pulmonary nodule (four cases; Figure 4) and of a neoplastic adrenal nodule with chromogranin expression (one case); study of pleuropulmonary masses (two cases), showing diffuse expression of calretinin (Figure 5); PAS special stain for an area of cardiac fibrosclerosis related to a past myocardial ischaemia (two cases); identification of heart damage due to sternal puncture (one case); demonstration of dissection of the aortic vessel with haemorrhage in the tunica media and disrupted elastic

lamellae (one case); demonstration of liver damage from a transbronchial probe during lung biopsy (one case; Figure 6); PAS staining to demonstrate the presence of intra-alveolar deposition compatible with hyaline membranes (three cases); and using Perls' stain to identify asbestos fibres in lung tissue (two cases) by obtaining new 30 μm tissue sections (instead of standard 3–5 μm tissue section) from paraffin blocks in order to enhance sensitivity of the technique and to avoid false-negative results (Figure 7).

Discussion

In our study, consultation between forensic and clinical pathologists for histopathology referrals examination after forensic autopsies was necessary in 11% of the forensic autopsies reviewed. The consultation was requested for primary sampling (10% of cases), secondary gross sampling (resampling; 12%), histopathological analysis (60%), IHC analysis (31%), special stains (21%) and molecular analysis (8%). Notably, a lack of systematic sampling of bone marrow was revealed. In the remaining 89% of cases, the overall evaluation of the scene of death and anamnestic data, coupled with the macroscopic findings at post-mortem examination, were sufficient to determine the cause of death, and no histopathological investigation was required.

In the forensic community, there is no consensus with regard to the need to perform systematic histological examination during forensic autopsies. This detail also seems dependent on the fact that the literature on this topic is limited. In the literature, one of the most important points that seems to arise is that whether histology, with or without the support of ancillary techniques, will be required depends primarily on the pathologist who performs the autopsy, regardless of the forensic or clinical reason for the post-mortem examination.

Since forensic pathologists are mainly concerned with the identification of the cause and manner of deaths that occurred in violent circumstances, histopathological analysis would often not provide additional information. Conversely, clinical pathologists stress the importance of histopathological analysis because this can very often provide information on the mechanism of death, while at the same time aiding the identification of possible traumatic, inflammatory or neoplastic co-morbidities that affected the deceased and which may have caused or contributed to the death.[3]

Generally speaking, forensic pathologists are inclined to believe that histopathological analysis should be undertaken only if it will provide additional relevant information. According to the Standards for the Practice of Forensic Pathology by the Forensic Pathology Committee of the College of American Pathologists, the histopathological examination of autopsy tissues is at the discretion of the clinical pathologist.[4] According to the Forensic Autopsy Performance Standards of the National Association of Medical Examiners, 'the forensic pathologist shall perform histological examination in cases with no gross anatomic cause of death'.[5]

The Code of Practice of Forensic Pathology in England, Wales and Northern Ireland (2012) states that 'a histopathological examination should be made, by the pathologist himself, of the major organs (assuming that they are not heavily decomposed) in all cases'.[6] Between 2015 and 2019, the Royal College of Pathologists in the UK issued detailed guidelines on best practices for autopsies under different circumstances of death. These encompass deaths in patients with epilepsy, including sudden deaths, autopsies after tissue and organ donation, postoperative deaths, neonatal death, autopsy when drugs or poisoning may be involved, bodies recovered from the water, aviation-related fatalities, suspected acute anaphylaxis, industrial and/or occupational-related lung disease deaths, including asbestos exposure, third-trimester antepartum and intrapartum stillbirth, foetal autopsy (second trimester foetal loss and termination of pregnancy for congenital anomalies) and sudden death with likely cardiac pathology.[7] All the aforementioned guidelines and recommendations are summed up in Figure 8 and compared with our major findings.

Autopsy practice is different in the educational setting (for the most part, see the US graduate medical education programme requirements in forensic pathology) which set out that 'a forensic pathology fellow must complete a minimum of 200 "complete" autopsies during the fellowship with histopathology examination' (Accreditation Council for graduate medical education).

Concerning the need for histopathological investigations in all cases, in a retrospective study of 500 adult forensic cases, Fronczek et al. discussed the role that microscopic analysis played in determining the cause of death. Of the 500 cases, histology was undertaken in 287 (58%) cases. Microscopic examination provided the cause of death in just 2% of cases where histology had been undertaken, while it added to the cause of death in 8% of those cases. In 61% of the cases, microscopic examination confirmed the macroscopic findings. In 30% of the cases, it did not influence the cause of death determined medically. The authors concluded that practice guidance should be adjusted to reflect this fact. While histological examination may be essential in certain circumstances, the decision to retain material for histology should be made on a case-by-case basis at the pathologist's discretion.[8] In contrast, De Giorgio et al. state that the discretion in

the decision of performing histopathology would be contrary to the position adopted by the Council of Europe, since it would introduce (a degree of) uncertainty which would be hard to reconcile with the need of the courts to be able to trust fully all evidence presented in order to protect the innocent.[9]

The data from our audit also agree with a retrospective study performed on 638 autopsy cases by Langlois et al., who reported that histopathology provided a relevant contribution in identifying the cause of death in 53% of cases.[10] The importance of histopathology was also demonstrated by Bernardi et al., who found that the lung and liver were the organs with the most frequent discrepancies between gross and microscopic findings in a series of 371 hospital autopsies.[11] Roulson et al. reported that >20% of clinically unexpected autopsy findings can be correctly diagnosed only by histopathological examination. Thus, when macroscopic analysis is performed, it should be matched by routine histology.[12] Moreover, Zaitoun et al. found that histopathological examination contributed significantly to the final diagnosis in a series of 108 hospital autopsies.[13]

This study confirms the above opinions. Although many post-mortem diagnoses are macroscopically evident by the end of dissection, histopathology can provide, modify or confirm the cause of death in a substantial number of cases. In this regard, it is important for forensic pathologists to document all histopathological findings, describing relevant positive and negative macroscopic and microscopic features and submitting appropriate specimens for histopathology, including at least samples of the heart, lungs, liver, kidneys and stenotic coronary arteries, as well as any macroscopically abnormal tissues,[10] including specimens from the central and peripheral nervous system.[14]

Based on the above considerations, it is clear that collaboration among forensic and general pathologists is needed. According to Madadin et al., in a case where the histological assessment of the autopsy specimen is undertaken by a pathologist other than the one who dissected the body and collected the samples, standard operating procedures need to be developed to minimise the risk of lowering the overall quality of the autopsy.[15] As they state, 'histopathology as an important aspect of a high standard medicolegal death investigation is not disputed'.

In some parts of the world, forensic pathologists who perform autopsies do not have sufficient histopathology training for adequate microscopic evaluation of tissue samples. In those circumstances, it is strongly advised that forensic pathologists establish robust working relationships with a surgical or hospital based histopathologist to be able to deal with this aspect of the death investigation.

In Italy, post-mortem examination can be instructed by a prosecutor of the court if the circumstances are connected to a crime such as homicides, violent cases, unnatural deaths, deaths during operations, deaths caused by an industrial disease or industrial poisoning and others. In these cases, a forensic pathologist who undertakes the post-mortem is chosen by the prosecutor in order to establish the cause, the manner and the time of death. Post-mortem examination can be performed by a clinical pathologist if there are no criminal implications, but only to know the cause of death. A post-mortem by a clinical pathologist is carried out if the cause of death is unknown, the person who died was not seen by a medical practitioner during their final illness, the death was sudden and unexplained or the medical certificate is not available. In our department (University of Verona), a cooperation between forensic and clinical pathologists has started, in order to enhance and share knowledge and to improve the overall competency of both groups. Reporting from our experience of 4 years of collaboration has shown that in 89% of medico-legal autopsies, there was no need for histopathology consultation. Conversely, in the remaining 11% of cases, a close cooperative relationship was of great value.

Conclusion

Consultation among forensic pathologists and clinical pathologists for histopathology examination may be necessary in around 11% of forensic autopsies. This includes gross re-sampling tailored to answer specific questions, evaluation of nodules suspected to be neoplastic and performing additional special stains, IHC and molecular analysis. On this basis, the cultivation of cooperative relationships at all levels is needed among forensic pathologists and general pathologists. This collaborative cooperation should be encouraged in order to improve education, standardisation and the quality of procedures. In conclusion, this paper has shown that the issue is not merely one of determining whether histopathological examinations are necessary in all cases. Instead, efforts should be made to implement useful guidelines and suggestions based on real-world routine practice, which lead to the clear identification of those cases where histopathology will provide important and beneficial information, which, in our experience, will include at least 11% of all cases.

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Declaration of conflicting interests

The authors hereby state that they have no conflicts of interest with any of the agencies or entities involved with or cited in this paper.

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