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Case Report

When a death apparently associated to sexual assault is instead a natural death due to idiopathic hypereosinophilic syndrome: The importance of gamma-hydroxybutyric acid analysis in vitreous humor

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ABSTRACT

We here report a case involving a 21-year-old female, found dead in a central square of a city in the south of Italy. Initial evidences and circumstances were suggestive of a death associated with a sexual assault. Two peripheral blood and two vitreous humor samples were collected for the purpose of gamma-hydroxybutyric acid (GHB) testing from the dead body at two different post-mortem intervals (PMIs): approximately 2 (t_0) and 36 (t_1) hours. The obtained results showed that, between t_0 and t_1, there was an increase of GHB concentrations in peripheral blood and vitreous humor of 66.3% and 8.1%, respectively.

This case was the first evidence of GHB post mortem production in a dead body and not *in vitro*, showing that vitreous humor is less affected than peripheral blood in GHB post-mortem production.

The value detected at t_1 in peripheral blood (53.4 μg/mL) exceeded the proposed cut-off and if interpreted alone would have led to erroneous conclusions. This was not the case of vitreous humor GHB, whose post-mortem increase was minimal and it allowed to exclude a GHB exposure.

Only after a broad forensic investigation including a complete autopsy, serological, histological, toxicological and haematology analyses, a diagnosis of idiopathic hypereosinophilic syndrome, a myeloproliferative disorder characterized by persistent eosinophilia associated with damage to multiple organs, was made and the cause of death was due to a pulmonary eosinophilic vasculitis responsible for an acute respiratory failure.

1. Introduction

In all cases of homicides, suspected homicides and other suspicious deaths, it is crucial for the forensic pathologist to be at the scene of death before the removal of the body, to inspect the crime scene, the local circumstances, the position and the condition of the dead body [1].

Very often crime can be quickly excluded because in the majority of cases death is caused by accident, suicide or even natural causes [1]. However, the latter occurrence cannot always be promptly recognized and only after further investigations the eventual natural cause of death can be identified.

When deaths associated with sexual offences occur, among the corollary of investigations necessary in these cases, special attention should also be paid to the eventual presence of drugs which may have facilitated sexual assault.

Drug-facilitated sexual assault (DFSA) is a condition that happens when a subject (male or female) is exposed to sexual act(s) while incapacitated or unconscious because of psychotropic drugs effects, resulting in being unable to resist such actions. The intended victim may have taken these substances unknowingly, or the abuser may have taken advantage of a victim who had voluntarily ingested one or more of them [2]. In certain cases these substances may also have played a role in determining death. Therefore their identification and quantification in biological fluids of the victim represent an important issue to correctly solve a fatality case.

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We here report a case involving a 21-year-old female, found dead in a central square of a city in the south of Italy. Initial evidences and circumstances were suggestive of a death associated with a sexual assault. Only after a broad forensic investigation including a complete autopsy, serological, histological, toxicological and haematology analyses, a diagnosis of idiopathic hypereosinophilic syndrome, a myeloproliferative disorder characterized by persistent eosinophilia associated with damage to multiple organs, was made.

2. Case report

A 21-year-old female, who lived underground in Italy and worked as a street prostitute was found in a spring early morning (6 a.m.) partially naked with exposed genitals next to a rubbish bin in an urban area of the southern Italy. Outside temperature was about 18 °C. Post mortem interval (PMI) was established according to the Nomogram Method of Henssge which is based on a single measurement of the rectal temperature [3]. The estimation of PMI was about 2 h. A complete autopsy was performed approximately 36 h after death. During the external examination only a bruise of a 1.5 cm diameter was detected on the root of the right inner thigh. No further significant findings were highlighted. The autopsy did not reveal any traumatic lesions or signs of sexual abuse, all the other organs were unremarkable only a polyvisceral congestion was notable. The bladder was empty.

As in all suspected cases of sexual assault a rectal and a vaginal swab were collected for the identification of spermatozoa, which were both negative. Moreover, in order to ascertain whether the alleged rape occurred under the influence of drugs, a broad toxicological investigation was carried out, giving special emphasis to drugs usually implicated in sexual assault, such as GHB. Regarding the latter, taking into account the post-mortem production of this substance, a novel approach based on the collection of biological samples from the body at two different PMIs was performed as follows:

Three peripheral blood and two vitreous humor samples were collected at two different PMIs: one blood and one vitreous humor samples at the scene of death (t_0, approximately 2 h after death) and two blood and one vitreous humor samples during the autopsy (t_1, approximately 36 h after death). After collection, two peripheral blood and two vitreous humor specimens were immediately stored at −20 °C until analysis and no preservatives were used. The third peripheral blood sample was preserved with sodium fluoride for the determination of alcohol by head space gas chromatography coupled to a flame ionization detector (HS-GC-FID) using an in-house fully validated method.

A general screening for drugs of abuse by liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) was performed on no preserved t0 blood sample as described elsewhere [4]. Moreover, both in t_0 and t_1 blood samples gamma-hydroxybutyric acid (GHB) was measured by GC–MS after liquid-liquid extraction according to a previously published method [5]. Finally, the analysis of GHB in t_0 and t_1 vitreous humor samples was performed according to the method below reported.

For histological analysis the following samples were collected and fixed in 10% neutral buffered formalin: brain, lung, heart, liver, kidney and bone marrow. After fixation, all samples were paraffin-embedded, sectioned at 6 μm thickness and stained with hematoxylin and eosin.

Serological testing for anti-HIV-1/2, anti-HCV, HBsAg, and anti-HBc and parasitic infections as well as a complete blood count (CBC) were performed on blood collected on the scene.

3. Toxicological analysis

3.1. Sample extraction

To 100 μl sample (calibrators and controls), 1 mL deionized water, 5 μL GHB-d_6 (100 ng/μL), 1 mL sodium acetate buffer 1 M (pH 5) and 4 ml ethyl acetate were added. The samples were mechanically mixed (vortex) for 1 min and then centrifuged for 3 min at 4000 rpm. The upper organic layer was carefully transferred to glass test tube and evaporated to dryness under nitrogen at room temperature. Then, 50 μL of BSTFA + 1% TMCS were added to the dried extract and analytes derivatized for 30 min at 70 °C.

3.2. Instrumentation

GC analysis for vitreous humor GHB was carried out on an Agilent HP 7028A GC gas chromatography instrument coupled with an Agilent MSD 5975 (Agilent Corporation, Palo Alto, CA, US). The capillary column used was an HP-5MS (17 m × 0.25 mm I.D coated with a 0.25 μm film). The GC conditions were as follows: the column temperature was programmed from 80 °C to 290 °C with an increase of 15 °C/min; the injection port and the transfer line temperature was 270 °C; helium was used as carrier gas with flow rate of 1 ml/min; the split injection mode had a ratio of 5:1. The mass analyzer was operated by electron impact (−70 eV) in selected ion monitoring mode (SIM). Quantitative analysis was carried out recording ions *m/z* 117-147-233 for GHB and *m/z* 239 for GHB-d6. The underlined ions were used as quantifiers in quantitative analysis.

The method was validated according to the guidelines of Peters et al. [6]. Linearity, limits of detection and quantification, selectivity, carryover, precision, accuracy, recovery, and stability were determined. A 0.9% saline solution (NaCl) was used as vitreous humor surrogate matrix for quality control (QC) samples and calibrators preparation.

4. Results

4.1. Toxicological analysis

4.1.1. Method validation for GHB in vitreous humor

The GC–MS assay for GHB in vitreous humor resulted linear between 0.1–50 μg/mL with determination coefficient (r^2) higher than 0.990. Limit of detection (LOD) and of quantification (LOQ) were 0.03 and 0.1 μg/mL, respectively.

Using QC samples at 0.2, 10 and 40 μg/mL GHB in 0.9% NaCl, analytical recovery of the assay was always above 90%, intra and inter-day precision and accuracy always better than 15%. No relevant degradation was observed after any of the three freeze/thaw cycles with differences in the initial GHB concentration of less than 10%. Differences to the initial concentration always lower than 10% were obtained also for QC samples stored at −20 °C for three months, thereby confirming the validity of the samples stored for analysis.

4.1.2. Screening for drugs of abuse and alcohol

The screening of drugs of abuse by HPLC-MS/MS in peripheral blood was negative, whereas the determination of alcohol by HS-GC-FID gave a value of 0.2 g/L.

4.1.3. GHB concentrations in post-mortem peripheral blood and vitreous humor samples

The analysis of GHB in vitreous humor and peripheral blood samples collected on the crime scene (t_0, about 2 h after death) gave the following concentrations: 7.4 and 32.1 μg/mL respectively, whereas in vitreous humor and peripheral blood collected during the autopsy (t_1, about 36 h after death) were 8.0 and 53.4 μg/mL of GHB were found. The extracted ion chromatograms (EICs) obtained from the analysis of GHB in vitreous humor and peripheral blood at t_0 and t_1 are reported in Fig. 1.

4.2. Histological analysis

The histological analysis in lungs highlighted a vascular congestion and marked eosinophil recruitment with signs of degranulation.

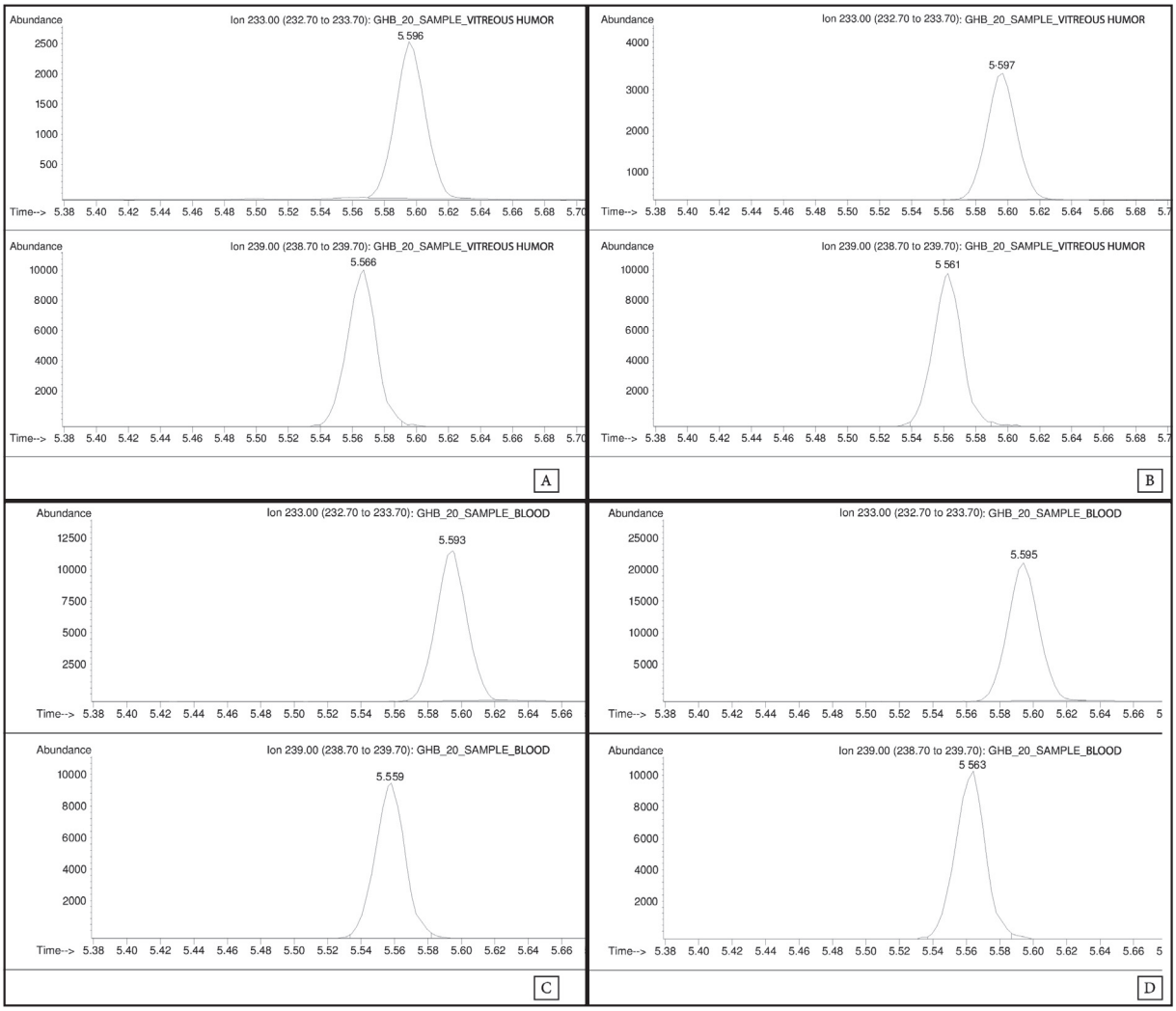

Fig. 1. Electron Impact Chromatograms obtained from the analysis of GHB in vitreous humor at t_0 (A) and t_1 (B) and peripheral blood at and t_0 (C) and t_1 (D). The following ions *m/z* 233 for GHB and *m/z* 239 for GHB-d6 were used as quantifiers in quantitative analysis.

Moreover, there was also evidence of vasculitis with eosinophil recruitment and focal intimal myofibroblastic thickening. In the heart a mild interstitial eosinophilic infiltration was present and in the liver there was a cloudy swelling of hepatocytes which show granular cytoplasm and focal eosinophilic infiltration of fibrotic and thickening portal spaces. In kidney samples a diffuse and marked vascular congestion and cloudy swelling of cortical convoluted tubules was observed. A diffuse eosinophilic infiltration of renal pelvis was also noticed (Figs. 2 and 3). Brain samples showed only a severe oedema.

The bone marrow showed normal hematopoietic components with prevalence of eosinophilic granulocytes in the myeloid series.

4.3. Serological and haematological analyses

The serological analysis was negative for viral (HIV, HBC, HCV) and parasitic infections. The CBC results performed on the blood sample collected about 2 h after death is reported in Table 1.

5. Discussion

GHB has received significant attention in the last two decades for its frequent implication in DFSA cases due to its bimodal euphoric-sedation effects [7,8]. Indeed, the expression “GHB-facilitated sexual assault” (GHB-FSA) has very recently been coined referring to “the intentional administration of GHB by the offender(s) to a victim usually, but not exclusively, in a dating context in the form of a colorless and odorless liquid or a white powder. In this way, it can easily be added to a drink with the victim being unaware of its presence, and after, under the effects of GHB-related intoxicated state, the victim is forced to have sex” [9]. GHB has been implicated in a rising number of deaths, therefore its determination and the correct interpretation of the amount detected is an important task for all forensic toxicologists dealing with this issue [10].

The determination of GHB has been carried out not only in conventional matrices such as blood and urine [8,11], but also in alternative matrices e.g. hair [12–14]. For other matrices, such as vitreous humor, only few studies are presently available [11,15,16].

In post-mortem settings, it is of vital importance to be cautious when interpreting GHB values, for the possibility of its post-mortem production associated with microbial action phenomena and autolysis [17,18].

Setting GHB cut-off values in biological samples is necessary to differentiate endogenous production from exogenous exposure and 50 μg/mL has been proposed as a cut-off to discriminate endogenous production from active consumption [17,18]. However, as already demonstrated by Korb and Cooper [19], this cut-off value cannot unanimously be applied. In any case; analytical alternatives to discriminate endogenous form exogenous GHB exist using gas chromatography-combustion-isotope ratio mass spectrometry (GC-C-IRMS). Significant differences in the carbon isotopic ratio (delta(13)C-values >

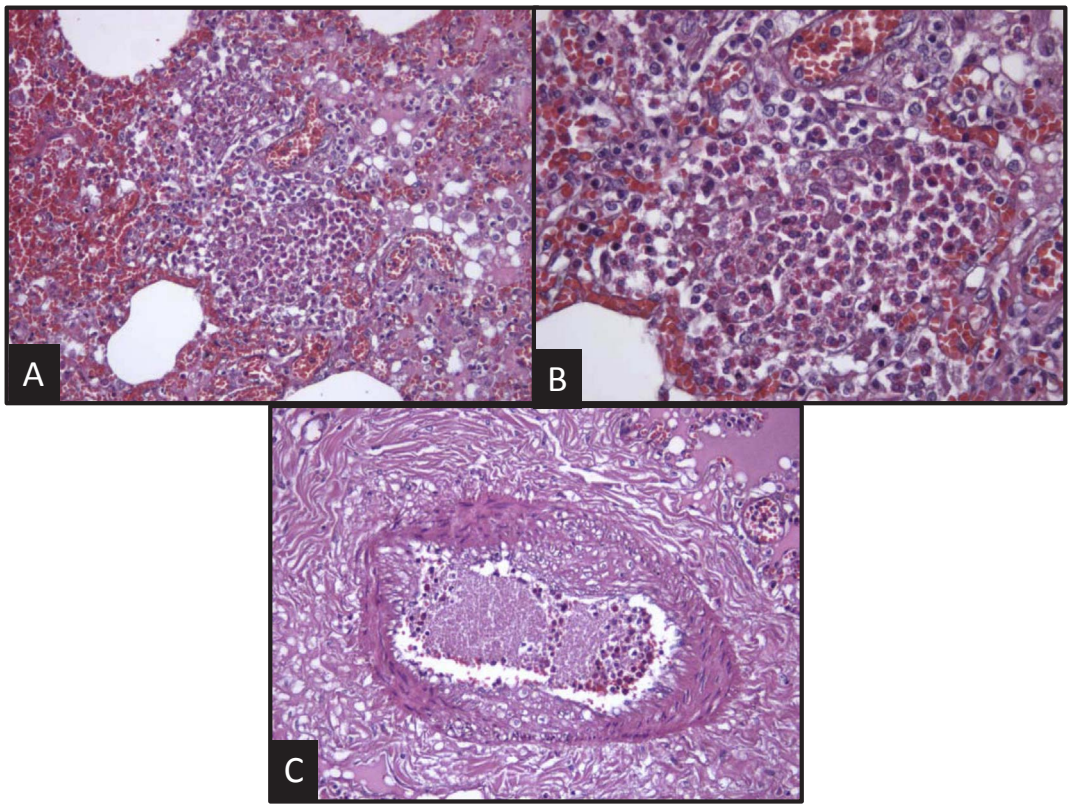

Fig. 2. Lungs: Vascular congestion and marked eosinophil recruitment with signs of degranulation (A and B), H & E original magnifications 40× and 60×. Evidence of vasculitis with eosinophil recruitment and focal intimal myofibroblastic thickening (C), H & E original magnification 20×.

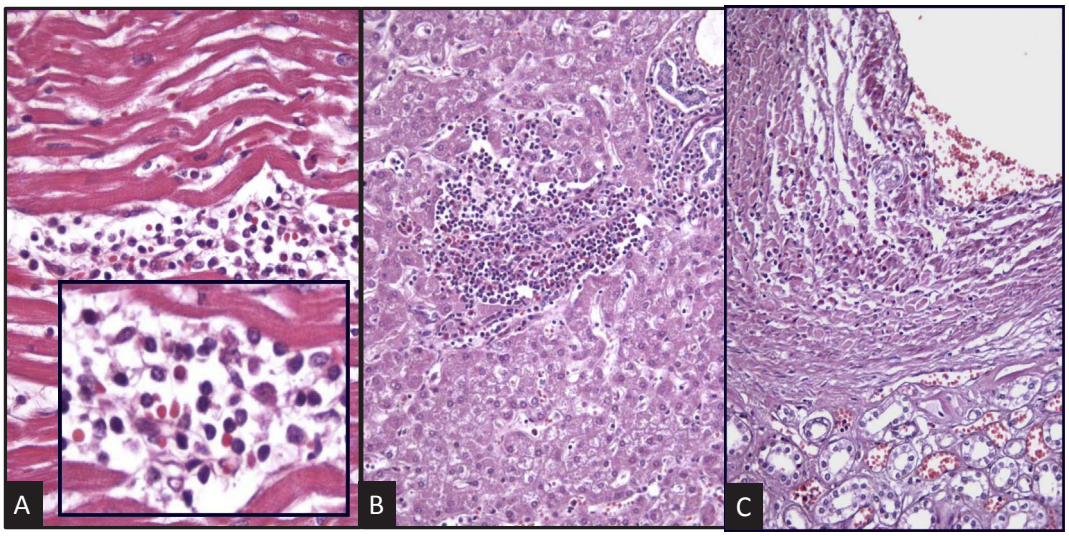

Fig. 3. Mild interstitial eosinophilic infiltration of cardiac muscle (A), H & E original magnification 40×. Moderate interstitial eosinophilic infiltration of liver (B), H & E original magnification 20× and renal parenchyma (C), H & E original magnification 20×.

13.5 per thousand) were found between endogenous and exogenous providing an unambiguous indication of the drug origin also in post-mortem [20].

In the case here reported, two peripheral blood and two vitreous humor samples were collected for the purpose of GHB testing from the dead body at two different PMIs: approximately 2 (t_0) and 36 (t_1) hours. The obtained results showed that, between t_0 and t_1, there was an increase of GHB concentrations in peripheral blood and vitreous humor of 8.1% and 66.3%, respectively.

This case was the first evidence of GHB post mortem production in a dead body and not *in vitro*, showing that vitreous humor is less affected than peripheral blood in GHB post-mortem production.

The value detected at t_1 in peripheral blood (53.4 μg/mL) exceeded the proposed cut-off and if interpreted alone would have led to erroneous conclusions. This was not the case of vitreous humor GHB, whose post-mortem increase was minimal.

Taken together, the differences in GHB concentration in the two examined biological matrices demonstrate that:

- It is important to collect biological samples as soon as possible after death if the suspect of GHB involvement is plausible;
- Vitreous humor may represent a valid complementary biological

Table 1
CBC performed on peripheral blood sample collected about 2 h after death (t_0); a marked hypereosinophilia is highlighted.

Complete Blood Count	Blood collected at t_0
Red blood cell	3,000,000/mm^3
Haemoglobin	10.2 g/dl
Haematocrit	30 %
White blood cell	9,500/ mm^3
Neutrophils	4,800/ mm^3 (50 %)
Lymphocytes	1,040/ mm^3 (10.5 %)
Monocytes	800/ mm^3 (8.5 %)
Eosinophils	**2,840/ mm^3 (30.8%)**
Basophils	20/ mm^3 (0.2 %)
Platelets	140,000/ mm^3

matrix to exclude erroneous deduction concerning GHB intake, even though this evidence derives from only one single case and at present there are no general accepted cut-offs for GHB in vitreous humor.

The toxicological approach adopted in the case here discussed, allowed to exclude a GHB exposure and therefore a DFSA case.

The histological analysis of samples collected during autopsy highlighted a multi-organ eosinophilic infiltration (Figs. 2 and 3), especially in the lungs where the evidence of vasculitis with eosinophil recruitment and focal intimal myofibroblastic thickening was also notable, moreover CBC performed on the blood sample collected at t_0 had highlighted a marked hypereosinophilia (2840/mm^3, 30.8% of white blood cells).

The histological findings together with haematological analysis allowed us to diagnose HES.

HES is a rare disorder characterized by a sustained overproduction of eosinophils, peripheral eosinophilia, and tissue eosinophilic infiltration. It commonly affects the heart, lung, skin, and central and peripheral nervous systems, and often causes impaired organ function [21].

Until the late 1990s, this disease had a bad prognosis with a median survival of less than one year with less than 20% of patients surviving two years, and with death usually occurring because of organ dysfunction. Current treatment has fortunately improved the prognosis [21–23].

In this case, however, because of the fact that this young street prostitute lived underground, no information on the clinical development of the pathology which led to her death exists and without any medical treatment the prognosis of this illness could not improve. As the haematological examination is from a single sampling it is not possible to document the duration of this marked hypereosinophilia, notwithstanding the histopathological examination has highlighted an eosinophilic pneumonia with ongoing eosinophilic endovasculitis responsible for an acute respiratory failure, which can be identified as a plausible cause of death.

Podjasek and Butterfield [24], who conducted a retrospective review of the morbidities and causes of death in HES patients at Mayo Clinic, have examined 23 fatal cases and the most common cause of death was cardiac in 65% of cases, whereas pulmonary vasculitis was identified only in one case, making the latter very rare. Literature review also confirms the predominant cardiac involvement (Loffler endocarditis) among HES fatalities with respect to all other causes of death [24,25].

In the case here reported, however, only a mild interstitial eosinophilic infiltration of the heart was found in the absence of signs of myocardial infarction, therefore the predominant involvement of the heart can surely be excluded.

HES has been classified into primary (neoplastic), secondary and idiopathic according to a consensus proposal on criteria and classification of eosinophilic disorders and related syndromes [23], and in this case, the absence of a specific aetiology taking also into account the results of the serological analysis which was negative both for viral (HIV, HBV and HCV) and parasitic infections, allowed us to define the HES as idiopathic.

6. Conclusions

The case here reported allow us to draw the following conclusions:

- In cases of suspected DFSA, especially GHB-FSA, it is useful to collect not only blood but also other biological fluids and vitreous humor seems to be a valid complementary matrix for this purpose.
- For the first time in literature post-mortem production of GHB has been investigated directly from the body and not *in vitro*, by evaluating two different biological matrix, peripheral blood and vitreous humor, at two different time intervals. For this purpose an "ad hoc" method for the determination and quantification of GHB in vitreous humor by GC–MS was developed and validated.
- According to these findings, vitreous humor for GHB analysis was likely to be a more stable matrix in comparison to blood to avoid false positive results although what emerged from this single case has to be possibly confirmed in other cases.
- The toxicological approach adopted for the case here reported, allowed us to exclude a GHB exogenous administration.
- A fatal case of idiopathic HES has been here described, although it was not possible to document the duration of the hypereosinophilia, which represents an important parameter in HES diagnosis.
- The cause of death is due to acute respiratory failure secondary to eosinophilic pneumonia with ongoing eosinophilic endovasculitisis, which is very rare.

Conflict of interest

None.

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