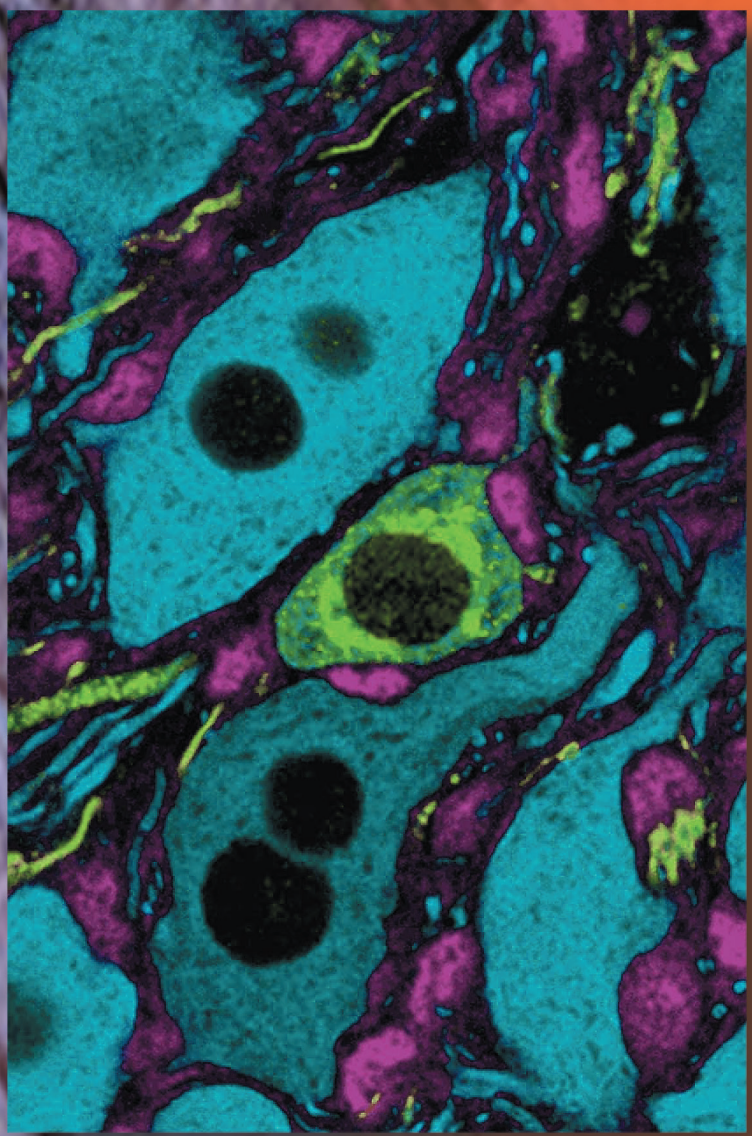
NOVEMBER 2020 VOL. 41 No. 4 Pages 120 - 151 AUSTRALIAN JOURNAL OF MEDICAL SCIENCE

AUSTRALIAN JOURNAL OF Medical Science

2020



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The Australian Journal of Medical Science is the official publication of the Australian Institute of Medical and Clinical Scientists (AIMS).

Circulation 2000 per issue. The Journal is circulated to members in pathology laboratories, universities and research institutes throughout Australia and overseas.

Annual subscription rates are available from AIMS National Office.

Article reprints may be organised on request from AIMS National Office.

Advertising rates are available from AIMS National Office.

Abstraction of the Australian Journal of Medical Science is through the following serial catalogue listings: Australasian Medical Index, Chemical Abstracts, and EMBASE/Excerpta Medica.

The Australian Journal of Medical Science is included on the Australian Research Council ERA 2018 Journal List.

ISSN 1038-1643

Printed by Westminster Eagle Eye Printing, PO Box 161, Paddington Qld 4064.

Design Cover and layout design by Kim Brown, 23 Denman St Exeter SA 5019 kimbo@internode.on.net. Cover photograph courtesy of Prof Ian Gibbins, Flinders Medical Centre, Adelaide.

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Analysis of cerebrospinal fluid for xanthochromia in the investigation of subarachnoid haemorrhage: experience of a state-wide, tertiary referral trauma centre

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Abstract

Subarachnoid haemorrhage (SAH) is spontaneous arterial bleeding into the subarachnoid space which is associated with high mortality and morbidity. To aid diagnosis, cerebrospinal fluid (CSF) can be examined for xanthochromia which is yellow discoloration, indicating the presence of bilirubin. The Department of Pathology offers a Monday-Friday (08:00-17:30), state-wide service for the detection of CSF xanthochromia. We audited our current service to assess clinical utility and the feasibility of offering a 24-hour laboratory CSF xanthochromia service. Seventy-eight CSF samples were received for xanthochromia testing from 2017-2018. There were no samples in which SAH was detected, and in one third of samples the patient was discharged prior to receiving the result. We estimated the base cost of offering a 24-hour CSF xanthochromia service would be $20,000, and the cost of analysing a sample out of working hours to be $2,600. Given the significant number of patients discharged prior to receiving the CSF xanthochromia result, a more targeted approach to the utilisation for this testing should be pursued.

Keywords: *Subarachnoid haemorrhage, bilirubin, xanthochromia*

Introduction

Subarachnoid haemorrhage (SAH) is spontaneous arterial bleeding into the subarachnoid space, which is associated with high mortality and morbidity. It is estimated that up to 10% of patients die immediately without any warning symptoms (Perry *et al* 2011). Furthermore, in the first six months after the event, mortality rates can approach 60% and survivors are often left with permanent neurological deficits (Lantigua *et al* 2015; Goyale *et al* 2016). Early diagnosis and treatment are therefore critical in reducing the otherwise high morbidity and mortality associated with SAH.

The diagnosis of SAH remains a diagnostic dilemma with no clear evidence for one investigation over another. Currently evidence suggests that there is close to 100% sensitivity for a negative Non Contrast-Computed Tomography of the Brain (NC-CTB) when performed within 6 hours of symptom onset. Beyond 6 hours the positive predictive value of a NC-CTB falls significantly enough (89%) that a negative scan cannot rule out a SAH (Carpenter *et al* 2016). On occasion, patients may warrant further investigation. These include (i) a very high pre test probability of SAH in the setting of a negative NC-CTB, (ii) a negative NC-CTB performed greater than 6 hours after symptom onset or (iii) an inconclusive NC-CTB. In those patients where further investigation is warranted, the most common next step is to perform a lumbar puncture (LP) for cerebrospinal fluid (CSF) xanthochromia and red blood cell (RBC) clearance. In patients with clinical symptoms suggestive of SAH, but a normal NC-CTB, the sensitivity of xanthochromia in CSF has been reported to be 100%, with a specificity of 75%, and a positive predictive value of 3.3% (Wood *et al* 2005). Given the low prevalence of SAH, it is suggested that 0.4% of LPs will be positive (Sayer *et al* 2015).

The Royal Hobart Hospital (RHH) is the largest public hospital in the state of Tasmania and provides a service to approximately 250,000 people in the southern region of the state. The Department of Pathology, RHH, is the only site in Tasmania providing a CSF xanthochromia service, which currently operates during normal working hours (Monday -Friday; 08:00-17:30) and offers an informal evening and weekend service (i.e. samples will only be analysed out of hours following discussion with the on call chemical pathologist and if trained scientific staff are available). The aim of this study was to audit our current service, and to assess the clinical utility of the CSF xanthochromia service

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on the management of patients with suspected SAH. We also wanted to assess the feasibility of offering a 24-hour laboratory CSF xanthochromia service.

Methods

We undertook a retrospective audit of CSF xanthochromia requests received from January 2017 to December 2018 (a period of 24 months). We reviewed laboratory results for all CSF xanthochromia requests. Data collected included the date and time of symptoms onset, presentation to the emergency department, initial NC-CTB scan, CSF sample collection, sample receipt in the laboratory, release of result to the clinician, and when the patient was discharged from the hospital. The presence of xanthochromia in CSF was determined by spectrophotometry using a GBC Scientific Equipment, UV/VIS 916 spectrophotometer (Braeside, Victoria, Australia), and results reported in accordance with international guidelines (Cruickshank *et al* 2008).

Results

Over the period studied, 78 CSF samples (one sample per patient) were received for the detection of xanthochromia with 95% of samples from the RHH and of these, 90% from the Emergency Department. Nine samples were not suitable for analysis due to either insufficient volume (i.e. less than 500µL of CSF received), or the sample was heavily blood stained (i.e. erythrocyte count > 40,000 x 10^6/L). Of the 69 samples analysed, there were no samples in which xanthochromia positively identified by spectrophotometry, including one equivocal result due to the presence of both bilirubin and oxyhaemoglobin.

The median (range) time from onset of symptoms to presentation at a hospital was 24 (1-672) hours. In eight (12%) samples the NC-CTB scan was undertaken within 6 hours of symptom onset (median 3, range 2-5 hours). Most (93%) LPs were undertaken within 12 hours to two weeks of symptom onset (median 32, range 10-241 hours), with five samples collected within 12 (median 4, range 8-10) hours.

Of the 69 samples analysed, 51 (74%) were analysed within normal laboratory working hours. The median (range) time for sample analysis and reporting of the result after receipt into the laboratory was 4 (1-66) hours, of which 35 (51%), and 13 (19%) were reported within three hours and one hour respectively. A third (15, 29%) of patients were discharged from the hospital 28 to 61 (median 20) hours prior to the CSF xanthochromia result being reported. The remaining patients were discharged from the hospital (median 13, range <1-410 hours) once reporting of CSF xanthochromia results was available.

The analysis of 18 samples, requested as urgent by the clinician, were conducted out of working hours. Once received in the laboratory, 13 (72%) samples were analysed and reported within three hours (median <1, range 1-3 hours), and four samples were analysed 4, 7, 11, and 41 hours after receipt into the laboratory. All patients were negative for CSF xanthochromia. In all patients the NC-CTB scan was undertaken after 6 hours of symptom onset (median 48, range 7-240 hours), and all except one patient were discharged after receiving the negative CSF xanthochromia result (median 3, range <1-282 hours). A single patient was discharged 30 hours prior to the CSF xanthochromia result being available.

Discussion

Our study confirms the low detection rate of SAH by CSF xanthochromia reported by other investigators who have found that less than 1% of patients where the NC-CTB scan was normal, CSF xanthochromia identified a SAH (Wood *et al* 2005; Goyale *et al* 2016; Bakr *et al* 2017; Ahmed *et al* 2017). Nevertheless, there remains the need for further investigations in some NC-CTB negative cases due to the high mortality and morbidity associated with SAH, especially if the NC-CTB scan is performed greater than 6 hours after the onset of symptoms - a time after which the sensitivity of CT for detecting SAH declines (Carpenter *et al* 2016).

We identified a significant number of patients being discharged prior to the xanthochromia result being reported. The natural conclusion here is that the test was inappropriately ordered, although through this audit, it is unclear why this might be the case. These findings do highlight the need for clinicians ordering investigations on CSF in the context of suspected SAH, to carefully consider which tests will support their clinical decisions and have the potential to influence the patient's management. Other investigators have also reported a large number (36 %) of inappropriate CSF xanthochromia requests (Goyale *et al* 2016). The cause in Goyale's study was deemed to be due to a confusing electronic requesting system - a cause that is not applicable to the audit undertaken here as an electronic ordering system is not currently in use within the hospital for pathology testing. Interestingly, patients where the sample was analysed out of working hours as an urgent request, were almost all (except one) discharged after receiving the result which therefore also suggests an economical incentive for expedited xanthochromia analysis.

Within the laboratory the analysis of CSF for xanthochromia by spectrophotometry is a technical and non-automated procedure that requires appropriately trained and experienced scientific staff. Given the relatively few CSF xanthochromia requests each year, it is not practical to train and maintain the competency of all scientific

staff in the assay. Therefore only a few scientists are trained in the assay procedure and interpretation, and although appropriately trained staff are usually available within normal working hours (i.e. Monday-Friday; 08:30-17:00), finding an available staff member to analyse an urgent sample outside of these hours is often difficult. Therefore, testing for CSF xanthochromia should not be considered as an automated and easily available assay by the requesting clinician.

A thorough cost-benefit economic analysis of spectrophotometry in the diagnosis of aneurysmal SAH is beyond the scope of this paper. However, in our organisation, the laboratory cost of analysing a CSF sample for xanthochromia is approximately $120 within normal working hours, which increases to $400 if a sample requires analysis out of hours. With regards to offering a formal 24-hour CSF xanthochromia service, we have estimated that the base cost would be approximately $20,000 per annum (excluding the additional $400 cost per sample of having the scientist attend on-site and undertake the analysis). This cost analysis is based on the additional reagents required, and predominantly the cost of having a staff member 'on-call' out of working hours. The cost of analysing the 18 out of working hours samples in this audit would therefore be $2,600 per sample. However an in-formal out of hours service continues to be provided.

Given the low diagnostic yield of LP for the identification of SAH, the laboratory resources required to analyse xanthochromia and that in samples analysed routinely, a third of patients were discharged prior to receiving the result, a more targeted approach to the utilisation of xanthochromia ordering should be pursued. In particular, the development of a more robust clinical pathway to select patients requiring further evaluation with a xanthochromia following a non-diagnostic or normal NC-CTB imaging. Benefits of this approach would be a reduction in the resources required to analyse samples, especially those out of routine working hours.

Conclusion

In patients presenting to the ED with suspected SAH, LP is still seen to have a role in the diagnostic workup despite a low diagnostic yield. Understanding when to order xanthochromia testing should be considered different to RBC clearance, and the test requested only if the clinician believes it will aid in patient management. Since xanthochromia testing is technical and non automated, further studies should be undertaken to understand the prevalence and cause of inappropriate xanthochromia ordering as well as to identify the subset of patients that will benefit from an LP as part of the investigation for SAH.

Acnowledgements

We thank Ms Julie Houston and Ms Janet Bartle for sample analysis, and Dr V Murdolo for advice on the draft manuscript.

Conflict of interest

There is no conflict of interest for this study.

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Papillary thyroid carcinoma with florid cutaneous metastases: management dilemmas

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Abstract

Thyroid malignancy is an uncommon cancer worldwide. Most patients with thyroid malignancy present with a long-standing history of midline neck mass which can be firm and hard on palpation. Selected cases may also present with hoarseness due to compression or direct infiltration of the recurrent laryngeal nerve. In this study we described the case of a sixty-one-year-old man who presented with huge anterior neck mass with overlying skin nodules for past the four months. Detailed investigation showed a papillary thyroid carcinoma and contrasted computer tomography (CT) of the neck revealed the mass had encased the carotid sheath and trachea as well as invaded the skin. We highlight the management issues faced in managing this type of rare case.

Keywords: thyroid gland, papillary thyroid carcinoma, extracapsular extension, cutaneous metastases, neoadjuvant chemoradiation

Introduction

Differentiated thyroid cancer arises from follicular cells of thyroid gland and it consists of papillary thyroid cancer and follicular thyroid cancer. Papillary thyroid carcinoma (PTC) is the most common thyroid carcinoma (80% of cases) and is prevalent in the third to fifth decade of life (Gimm *et al* 2001). It carries a good prognosis with 10 year survival rate of 98%. The older age patients i.e. more than forty-five-years-old and patients with extra-thyroidal extension and distant metastasis have reduced survival rate (Kim *et al* 2015). The main modality for thyroid mass investigation is by ultrasonography, a non-invasive procedure able to differentiate malignant thyroid mass from a benign nodule (Joseph-Auguste *et al* 2020). The risk stratification of malignancy based on ultrasound features, known as Thyroid Imaging Reporting and Data Systems (TIRADS), is used worldwide. It consists of a 6 point scale for risk stratification with increasing risk of malignancy (Russ *et al* 2017). Environmental exposure as well as diet and lifestyle are known to initiate epigenetic changes that relate to carcinogenesis in thyroid malignancy.

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Even though PTC grows slowly and has an indolent clinical course, recurrences are not uncommon averaging between 5 to 21% of cases (Wang *et al* 2019). The predictive factors that determine the recurrence include tumour stage, extrathyroidal extension and infiltration outside thyroid capsule, male sex, lymph node ratio, extranodal spread, multifocality and age (Wang *et al* 2019). The tumour commonly invades the adjacent structures including recurrent laryngeal nerve, trachea, larynx, oesophagus, sternocleidomastoid muscle, and internal jugular vein (Zhang *et al* 2019). Cutaneous metastases in a setting of thyroid malignancy are rare occurrence, accounting for only 1% of cases (Marquez Garcia *et al* 2016; Ferreres *et al* 2017; Dahl *et al* 1997). Among the histological types, PTC is the most common thyroid malignancy to present with cutaneous metastases.

Surgical removal of the tumour and metastatic lymph nodes remains as the primary treatment in differentiated thyroid carcinoma. Following the surgical excision, the treatment is continued with radioiodine therapy which aims to ablate residual tumours, and hence prevent recurrences (Kim 2015). However, in selected cases, aggressiveness of the tumour with infiltration to adjacent vital structures poses management challenges.

Case history

A sixty-one-year-old Malay man was referred to Otorhinolaryngology Head & Neck Surgery clinic for a

huge anterior neck swelling that had gradually increased in size over the past 20 years. In addition, he noticed development of multiple nodules and crusting of the skin overlying the swelling for the past four months. There was no history of traditional massage, prior history of radiation, trauma or chronic infection. There was no family history of malignancy or thyroid diseases. He denied any obstructive symptoms such as dyspnea, dysphagia, odynophagia or noisy breathing. He also denied any pain, hoarseness nor symptoms of hyper or hypothyroidism.

On examination there was a huge and a well-defined anterior neck swelling measuring 20.0cm x 11.0cm that extended from posterior border of sternocleidomastoid muscle to the contralateral sternocleidomastoid muscle. The mass was firm in consistency with multiple necrotic nodules on the overlying skin (Figure 1). There was no contact bleeding or discharge noted. Nasal-endoscopic examination showed no significant findings and 70-degrees laryngoscopy examination showed bilateral vocal cord was mobile and laryngeal inlet was patent without medialization of lateral pharyngeal wall.

An urgent fine needle biopsy was performed from two sites, the thyroid mass and the skin nodules. The result revealed a papillary thyroid carcinoma with skin infiltration (Figures 2 and 3). CT scan of the neck was carried out and showed a massive thyroid gland mass that extended from C5 to T3 vertebral level with local infiltration to the overlying skin and bilateral sternocleidomastoid muscles (Figure 4). The tumour also extended posteriorly to invade the prevertebral muscles. The mass effect had caused trachea deviation to the left and stenosis of bilateral internal jugular veins (Figure 5).

Combining all the findings together, we concluded that the tumour was so extensive with involvement of major critical structures, namely the trachea, carotid artery, internal jugular vein and skin that it was inoperable at this time. The patient was referred to the oncology team for neoadjuvant chemoradiation. At present he has completed radiation of 14 Gray and showed a good response (Figure 6). He will also receive chemotherapy with doxorubicin 75mg/m² every three weeks for total of six cycles.

Discussion

The diagnosis of thyroid malignancy has increased over the last decade due to improved diagnostic imaging techniques. It was the 14th most common cancer in women over last 20 years but is now seen as the 5th most common malignancy in women (Joseph-Auguste *et al* 2020). According to our local cancer registry, papillary thyroid carcinoma is the 7th most common malignancy among males and the 9th most common cancer among females in Malaysia (Azizah *et al* 2016). Thyroid malignancy usually presents as a painless anterior neck swelling which is firm on palpation. In many cases, patients only seek treatment after experiencing effects such as shortness of breath if the mass compresses the trachea, or dysphagia if it extends posteriorly and obstructs the oesophagus. In this case the patient only sought treatment due to the necrotic nodules over the neck despite having the neck mass for past two decades. In thyroid malignancy metastasis to cervical lymph nodes occurs in about 50% of cases. Distant metastasis is rare and usually the sites are lung, bone and liver. However, skin metastasis is extremely rare in papillary thyroid

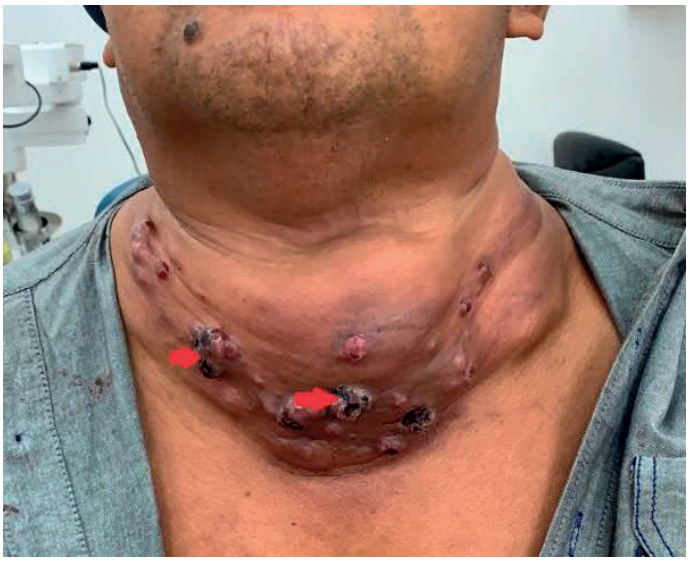

Figure 1. *Multiple skin nodules overlying massive thyroid papillary carcinoma with blackish necrotic and crusting foci (red arrows).*

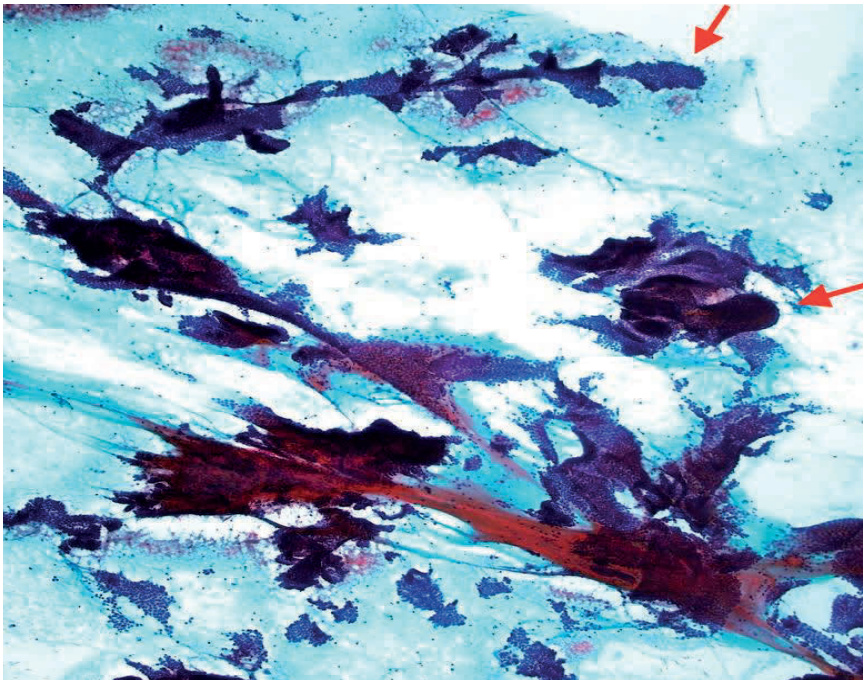

Figure 2. *The FNAC of thyroid gland composed of high cellularity exhibiting monolayer sheets and occasional papillary like fragments (red arrow) 40x (smear, Papanicolaou stain).*

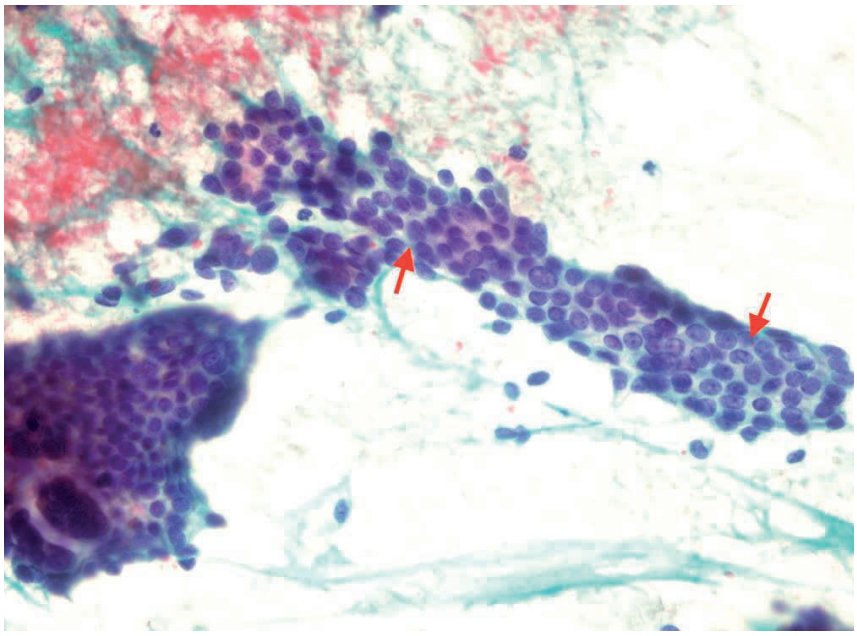

Figure 3. *Monolayered sheets of tumour cells with syncytial like-appearance. The cells composed of irregular nuclei, focal molding, nuclear grooves (red arrow), fine chromatin and micronucleoli 400x (smear, Papanicolaou stain).*

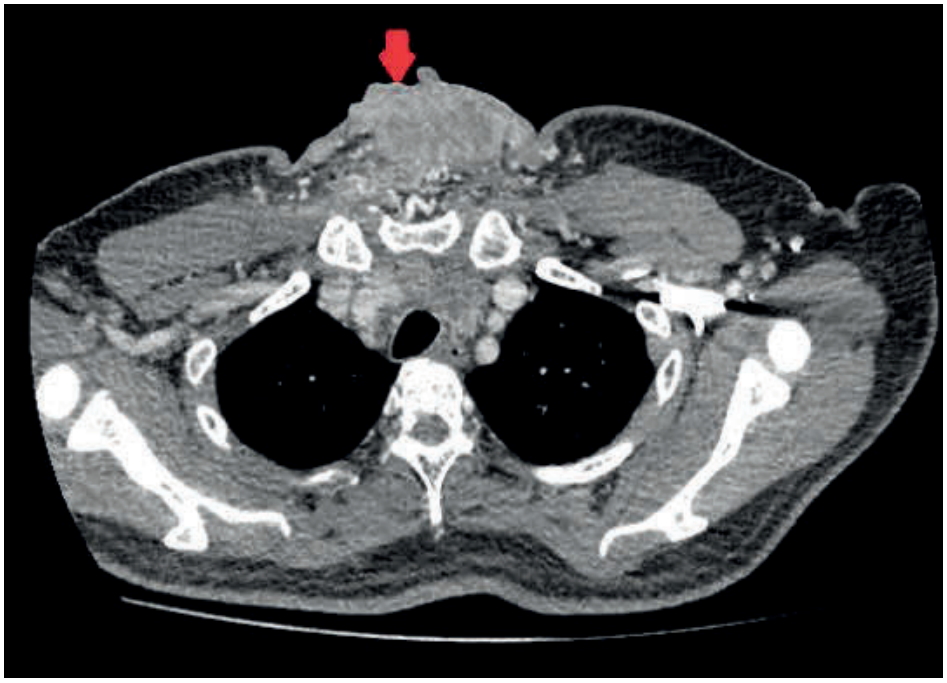

***Figure 4**. Axial cut of contrasted CT scan of neck showing a heterogenous neck mass with irregular nodular surface with skin invasion (red arrow).*

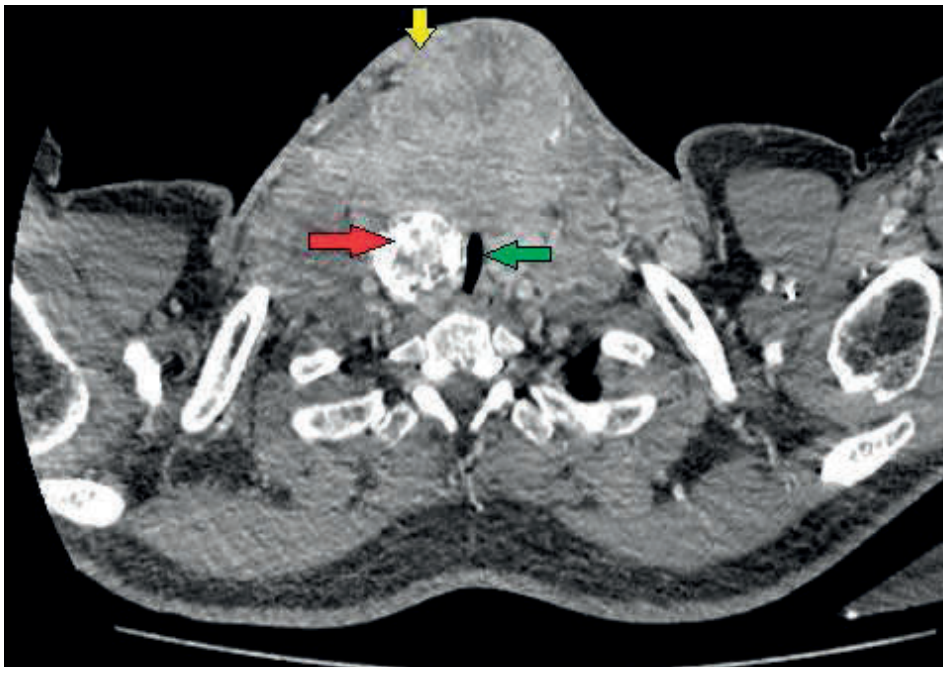

***Figure 5**. Axial view of contrasted CT scan of the neck showed a heterogenous large neck lesion with poor demarcation plane with underlying subcutaneous fat tissue (yellow arrow) and narrowing of airway (green arrow). There was calcification at right side of trachea (red arrow).*

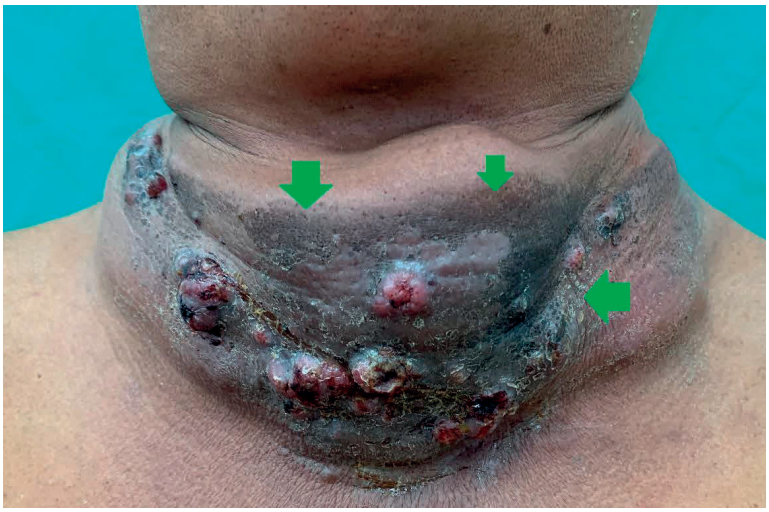

***Figure 6**. Thyroid mass after completion of radiation and two cycles of chemotherapy courses. The tumour mass has reduced in size with no new nodule appearance. There was skin hyperpigmentation due to post radiation effect (green arrows).*

carcinoma and can present as a slowly growing nodule or ulcer (Reusser *et al* 2014).

Cutaneous metastasis is an uncommon phenomenon in most solid malignancies. The most reported cases of malignancy to have cutaneous infiltration is breast carcinoma which tend to have chest metastases (Reusser *et al* 2014). In thyroid malignancy, cutaneous metastases have been reported to occur in less than 1% of cases (0.06-0.82%) (Reusser *et al* 2014). Different histological subtypes have different rates of cutaneous metastases, with the majority of cases occurring in PTC. The mechanisms that underlie cutaneous metastases include direct extension, implantation of tumour cells during fine needle aspiration cytology, biopsy or surgery, haematogenous spread and lymphatic spread. The cutaneous metastases have been reported to occur as a slow growing erythematous lesion, or mild erythematous nodules which may become ulcerated. In the majority of cases, the cutaneous metastases can be found on the scalp and head and face region due to rich vascularization as well as the neck, supraclavicular, back, forearm and flank (Marquez Garcia *et al* 2016; Ferreres -Riera *et al* 2017).

It is paramount to understand the clinical and surgical anatomy of the thyroid glands in relation to the surrounding structures, so that the clinician will be able to anticipate any complications arising from any pathology of thyroid gland. It will also help the surgeon to perform a refined surgical procedure with fewer morbidities. The thyroid gland is located at the midline of neck, overlying the second and third tracheal rings. Its size varies and generally it weighs about 20-25 grams. The thyroid receives blood from the inferior and superior thyroid arteries (ITA and STA), both being significant landmarks during thyroid surgery specifically thyroidectomy (Allen *et al* 2020). The recurrent laryngeal nerves (RLN) enter the posterior part of the gland inferiorly, very close to the inferior thyroid artery. The RLN can be located above, below or in between the branches of ITA. Thus, the ITA serves as a critical landmark to identify and preserve the RLN, in order to prevent RLN paralysis that can cause hoarseness. Lateral to the gland, the carotid artery, internal jugular vein and vagus nerve lie very closely to each other in the carotid sheath and are at risk of injury during thyroidectomy or neck dissections.

Surgical excision of tumour remains as the first line of treatment in papillary thyroid carcinoma. However, in certain cases, neoadjuvant external beam radiation and/or chemotherapy are required especially in extensive disease with invasion of the adjacent vital structures which can cause increased surgical morbidity. Neoadjuvant chemoradiation aims to shrink and downstage the tumour, making it operable for a total surgical extirpation. In addition, chemoradiation can prevent procedures such as tracheal resection, laryngectomy and oesophageal-pharyngeal resection (Dang *et al* 2016) that can significantly affect the patient's quality of life in post-operatively.

It is important to achieve a complete surgical resection as locoregional recurrence is the cause of death in the majority of patients. In addition, it is also essential to include the cervical-central compartment neck dissection to minimize the risk of locoregional recurrence (Gimm *et al* 2001). Therefore, radioactive iodine-131 ablation (RAI) treatment following tumour excision is necessary

to eliminate the remaining microscopic tumour cells that cannot be removed intraoperatively. It also benefited cases of thyroid cancer with neck nodes and distant metastasis.

Neoadjuvant therapy administration of therapeutic agents before a main treatment aims to reduce the size of tumour so that the surgical morbidities can be lessened. In thyroid malignancy, neoadjuvant therapy can be chemotherapy, radiotherapy or targeted therapy using tyrosine kinase inhibitor (Dang *et al* 2016). Neoadjuvant radiation is associated with risk of fibrosis which may lead to bleeding and difficulties in later surgery due to distortion of anatomical structures, abnormal vascularization and presence of significant fibrotic tissues. Thus, preoperative patient optimization and a proper surgical plan is crucial in overcoming these serious complications.

Neoadjuvant chemotherapy is rarely used due to limited benefit and high toxicity. It can be applied as monotherapy or as combination chemotherapy in the palliative setting. Doxorubin is commonly used. It is known as 'red devil' as it causes redness, swelling and painful redness of soles and palm, red urine, cardiomyopathy and skin and nail discoloration. Chemotherapy is a last treatment option and typically reserved for RAI refractory cases.

Conclusion

Aggressive thyroid malignancy is uncommon and limited disease can be cured with thyroid surgery plus neck dissection and adjuvant radioactive iodine ablation. In cases of extensive tumour with carotid arteries encasement and skin metastases, the issues of surgery need to be carefully weighed as high morbidities are expected from the surgery. Neoadjuvant chemoradiation can downstage the tumour and make tumour operable with fewer morbidities, providing patients with a better quality of life.

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ORIGINAL ARTICLE

Comparative analysis of platelet glycoprotein expression in whole blood and platelet-rich plasma

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Abstract

Platelet surface glycoproteins CD42a and CD62P are indicators of processes leading to platelet activation and aggregation. Quantitative assessment of the expression of platelet surface receptors by flow cytometry seems to be useful to detect prothrombotic changes of haemostasis. We compare the results of CD42a and CD62P expression detected by flow cytometric analysis between samples of whole blood (WB) and platelet-rich plasma (PRP) of 50 Caucasian healthy blood donors. In PRP, there is lower platelet reactivity and greater and potentially misleading influence of antiplatelet drugs. Comparative analysis of the co-expression of CD42a-fluorescein isothiocyanate (FITC) / CD62P-phycoerythrin (PE) in WB and PRP in healthy blood donors revealed that isolation of PRP affects platelet activation in a statistically significant manner ($p < 0.0005$). The reliability of platelet function testing can be improved by using WB.

Keywords: flow cytometry, platelet glycoproteins, platelet-rich plasma, whole blood, haemostasis

Introduction

Many platelet membrane receptors mediate signal sensing and the transmission of these signals is involved in the transport of various substances across the membrane. Besides the conventional receptors, platelet-specific glycoproteins (GPs) play an essential role on the surface of platelets. Alterations in the structure or function of platelet GPs may contribute to hemostasis disorders. Up to now more than 50 membrane GPs have been detected that mediate specific processes after binding site occupation. Receptors used to initiate activation and/or stimulation of mediators of hemostasis are also present on the platelet membrane (Clemetson 2015; De Cuyper *et al* 2013).

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CD42a (glycoprotein (GP) IX) is a 22-kDa transmembrane protein associated with CD42b, CD42c and CD42d to form the GP Ib-V-IX complex. Following an insult, an interaction between the GPIb-V-IX complex on the platelet surface with von Willebrand factor mediates platelet adhesion to subendothelial structures and contributes to their subsequent activation.

P-selectin (CD62P) acts as one of the cell adhesion molecules on the surface of activated platelets (Clemetson 2015; Staško *et al* 2011; Andrews and Berndt 2013; Evangelista and Smyth 2015). In non-activated platelets, P-selectin is stored in α-granules. In non-activated endothelial cells, it is stored in granules called Weibel-Palade bodies (McEver *et al* 1989). The expressed P-selectin is involved in elimination of activated platelets from the circulation and mediates adhesion of neutrophils and monocytes to endothelial cells and thrombi (Staško *et al* 2011).

Diagnostics of platelet-mediated disorders of haemostasis requires testing of platelet function with the aid of quantitative assessment of platelet surface receptors by flow cytometry (Nurden *et al* 2012). Flow cytometry is a technique that allows qualitative and quantitative analysis of optical and fluorescence characteristics of individual particles, mostly cells, in suspensions (Nieuwland and Sturk 2010).

We report on some clear and highly significant evidence of the usefulness of the preference of whole blood (WB) samples over platelet-rich plasma (PRP) in experiments detecting platelet activation by flow cytometry in humans. This study proves the advantages of the use of WB method to avoid any misinterpretations of results needed to make treatment decisions in patients affected by platelet function abnormalities.

Materials and methods

Our study included 50 Caucasian healthy blood donors – 62% (31) men and 38% (19) women, mean age of 34.5 ± 9.4 years (the youngest donor was 19 years old and the oldest was 59 years old) with no medication or chronic disease (e.g. without administration of calcium flux inhibitors or adenosine diphosphate (ADP) inhibitors). Further inclusion criteria were ages between 18-60 years old and agreement with participation in the study. Exclusion criteria were recent history of ischemic stroke and other clinically significant forms of thrombosis or increased risk of thrombosis associated with disorder of haemostasis, a quantitative or qualitative platelet disorder, and any relevant chronic disease requiring medication influencing the function of platelets.

In each of the included individuals, CD42a and CD62P expression in WB and PRP was determined in parallel using flow cytometry and temperature during the preparation of PRP was 22°C.

Blood samples were collected only in single-use vacutainer tubes with 3.2% (0.109 mol/l) sodium citrate as anticoagulant.

For the determination of CD62P in PRP, anticoagulated samples were centrifuged at 200g for 10 minutes, and the supernatant used. Platelet GPs were analyzed on a FACSVerse flow cytometer (Becton Dickinson & Co, San Jose, California). Fluorochrome-conjugated anti-CD42a/ fluorescein isothiocyanate (FITC) (clone SZ1, isotype mouse IgG1, Beckman Coulter, San Diego, USA) and anti-CD62P/ phycoerythrin (PE) (clone AC1.2, isotype mouse, IgG1, κ, Becton Dickinson) monoclonal antibodies were used for direct two-color surface immunophenotyping. For each sample, a minimum of 10,000 events were acquired and data were analyzed using the FACSuite acquisition / analysis software.

A typical example of CD42a and CD62P co-expression on platelets in WB (Figure 1 A,C) and PRP (Figure 1 B,D) is demonstrated in Figure 1. Two major gating strategies for platelet analysis were traditionally used. Platelets were either identified by their light scattering characteristics (population "Platelets" in Figure 1 A,B) or a combination of a gate in a scattergram and surface expression of a constitutive platelet marker (e.g. CD42a). Thus, in practice, when we detected the expression of CD42a by the FITC fluorochrome, we localized the platelets – based on this, we designed the gate. This gate was then used also for the detection of the coexpression of CD42a/CD62P. For the positive control, the activation of platelets with ADP with the final concentration of 10 uM (CD42a-FITC/CD62P-PE) was used. Negative control was performed with isotypic control IgG1/IgG2 (FITC/PE).

To illustrate our data, we chose quadrant statistical analysis of events gated in the platelet region in the forward scatter/ side scatter (FSC/SSC) dot plot as shown in Figure 1. As we used fluorescent probes FITC and PE for 2-colour flow cytometry, data for each antibody alone in WB and PRP separately are shown in Figures 2 and 3.

The relative proportion of activated (CD62P-positive, CD62P+) platelets within the whole platelet population was then calculated as the percentage of CD42a+CD62P+ events (Q2 in Figure 1 C,D) among all CD42a+ events (Q2 and Q4 events) gated as platelets in the FSC/SSC diagram ("Platelets"). The statistical analysis was performed using the statistical software STATISTICA, version 8. For the testing of the hypothesis, two types of tests were used – non-parametric paired Wilcoxon test for the comparison of two related samples and non-parametric Mann-Whitney test for the comparison of 2 independent samples. P value < 0.05 was considered as statistically significant.

All the work was conducted with the formal approval of the Ethics Committee of the Jessenius Faculty of Medicine in Martin.

All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

All measurements are reported using International System of Units (SI).

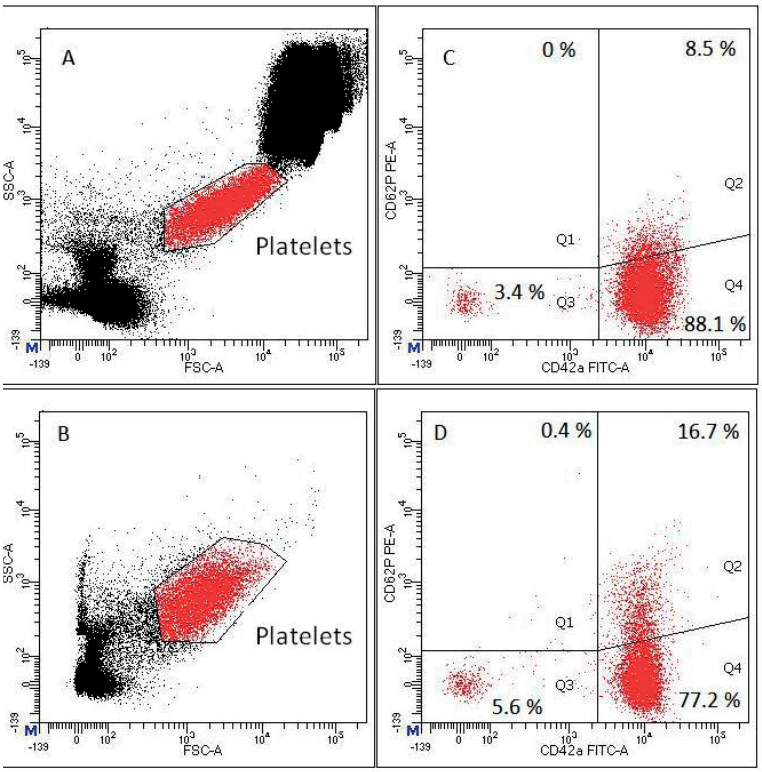

Figure 1. *Comparison of the expression of CD42a and CD62P by platelets in samples of whole blood (WB) (A and C) and platelet-rich plasma (PRP)(B and D)..*

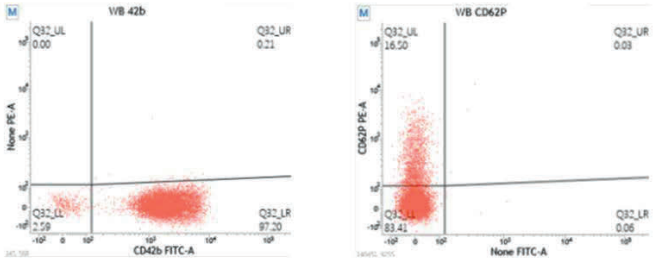

Figure 2. *Expression of CD42a and CD62P separately in WB.*

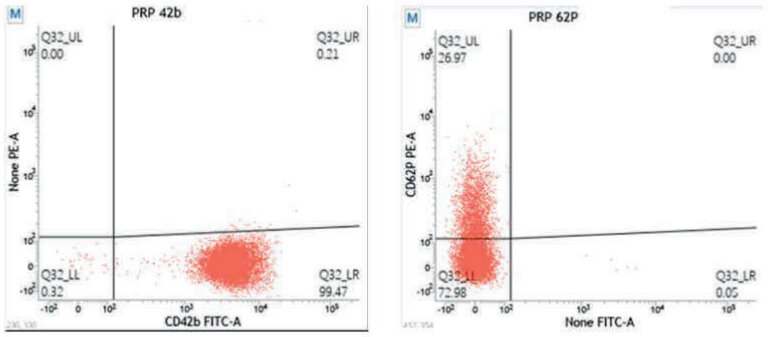

Figure 3. *Expression of CD42a and CD62P separately in PRP.*

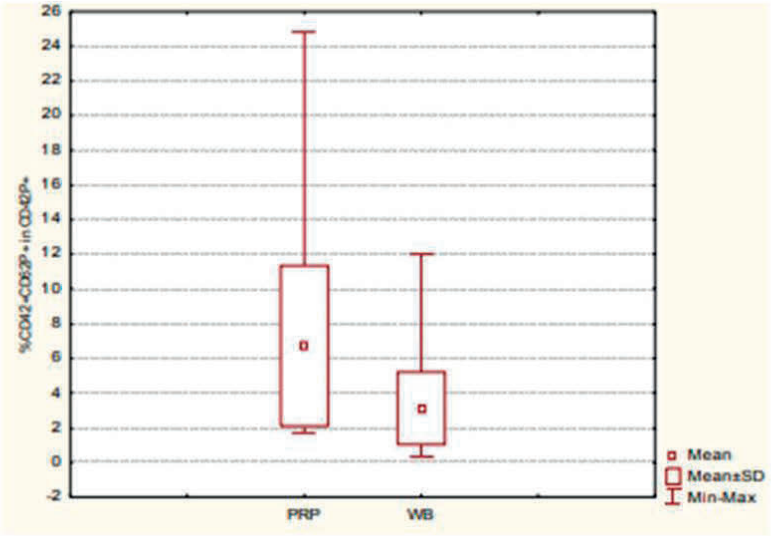

Figure 4. *Statistical analysis of activated platelet populations in PRP and WB samples of 50 healthy donors.*

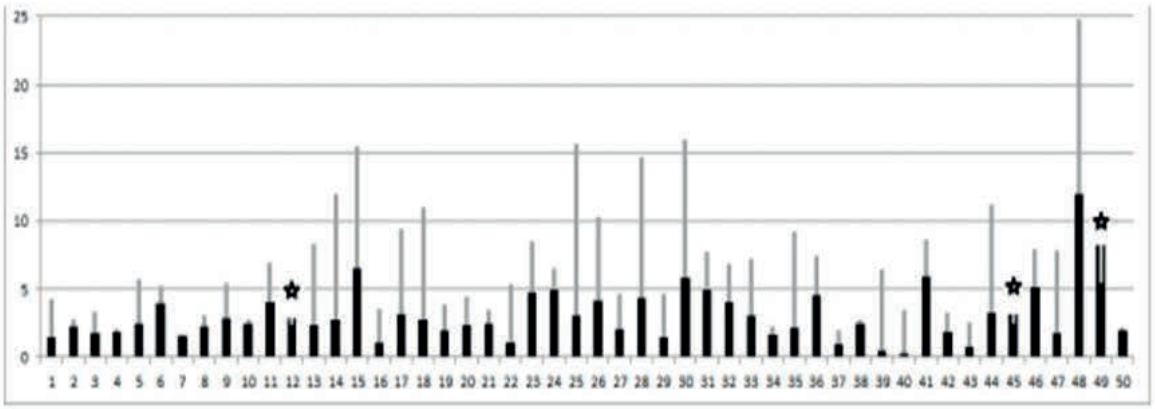

Figure 5. *Proportions of activated (CD62+) cells in the platelet (CD42a+) population in whole blood (black bars) and PRP (black bars plus grey lines) in individual donors.*

Results

In the example given in Figure 1, 8.8% (100% x 8.5 / (8.5+88.1)) and 17.8% (100% x 16.7 / (16.7+77.2)) of activated platelets were present in the WB sample and PRP respectively. Thus in the same blood sample, twice as many activated platelets were found in PRP compared with the WB sample.

Moreover, comparative analysis of the co-expression CD42a-FITC / CD62P-PE in WB and PRP in healthy blood donors revealed that isolation of PRP affects the platelet activation in a statistically significant manner ($p < 0.0005$) (Figure 4, Table 1).

Figure 5 shows results in individual donors. In individual samples, only three out of 50 samples exhibited the opposite profile with higher level of activated platelets in WB samples than in PRP, but there was only a small difference in all three cases and so could be considered as random events in terms of the small number error.

The decrease recorded in these three exceptions (donors 12, 45 and 45 in Figure 5, marked by asterisks) was quite small. We did not find any correlation between an increase of activated platelet numbers in PRP and the basal (WB) platelet activation status: in some cases with low basal (WB) activation (e.g. donors No. 1, 14, 18, 25, 30, 35, 44), the increase of activated platelet proportion was more than 100%, in other donors (e.g. No. 6, 24, 41) higher basal activation did not correspond to an excessive increase. In addition, a decrease from high basal activation was recorded in donor No.50. Overall, 3.57 +/- 3.51(%) more activated cells were found in PRP than in WB in individual donor analysis.

Discussion

Several studies that detected platelet activation markers with the use of flow cytometry on the samples of PRP have been performed (Augustine *et al* 2016; Akrawinthawong *et al* 2014; Yin *et al* 2017).

After the addition of thrombin in the lysed samples of WB, an increase in the activation of platelets was observed. Platelet activation could also be detected by flow cytometry showing the increased expression of CD62P. On the contrary, CD62P expression in PRP samples remained static. It is suggested that the preparation of PRP provokes premature platelet activation (Augustine *et al* 2016).

In the absence of the addition of an exogenous platelet agonist, WB flow cytometry may detect the activation state of circulating platelets by binding of an activation-dependent monoclonal antibody. Additionally to this evaluation of platelet function *in vivo*, involvement of an exogenous agonist in the procedure enables analysis of the reactivity of circulating platelets *in vitro*. Several studies assessed the correlation between data obtained from platelet ultrastructural analysis and activation of protein markers. Ultrastructural analysis with the use of scanning electron microscopy (SEM) is frequently performed in PRP samples (Tamimi *et al* 2007; Pretorius *et al* 2012). While various methods of PRP preparation have been registered (Fernández-Barbero *et al* 2006; Tamimi *et al* 2007; Pretorius *et al* 2008; Chandler, 2013; Headland *et al* 2014), the most common method for PRP preparation for SEM studies remains a single, high g-force centrifugation. A prominent limitation of platelet studies is the fact that sample preparation can lead to artifactual activation, deactivation,

	n	D	Sd	Median	min	max
PRP_% CD62P	50	6.7	4.6	5.5	1.7	24.8
WB_% CD62P	50	3.1	2.1	2.5	0.3	12.0

Wilcoxon´s test	Z	P
PRP vs. WB	5.777	< 0.0005

Table 1. *Statistical analysis of activated platelet proportions in platelet-rich plasma (PRP) and whole blood (WB) samples of 50 healthy donors. The difference between both groups of samples was statistically significant (p<0.0005). For the testing, non-parametric paired Wilcoxon test for the comparison of 2 related samples with the test statistics Z was used. P value < 0.05 was considered statistically significant.*

platelet aggregation or fibrin polymerization (Bolton-Maggs *et al* 2006; Picker, 2011) that can confound results.

In one study assessing the platelet activation during preparation of platelet concentrates, from the scale of several products, platelet concentrates derived from PRP showed the greatest differences with significantly higher concentrations of P-selectin ($p < 0.001$). Thus, WB flow cytometry is the more informative method for the evaluation of platelet concentrates (Metcalfe *et al* 1997).

Studies with flow cytometric assays of washed platelets or PRP are potentially susceptible to artificial *in vitro* activation of platelet due to the separation procedure (Berny-Lang *et al* 2013). In PRP, there is lower platelet reactivity and greater and potentially misleading influence of antiplatelet drugs when compared with WB. The reliability of platelet function testing could therefore be improved by using of WB (Madsen *et al* 2007). Flow cytometry with samples of WB reduces platelet manipulation and activation otherwise observed in the course of analysis with PRP. Additionally, it provides a more natural environment for detection, possibility of simultaneous detection of several platelet receptors, possibility to analyze also the samples with significant reduction in platelet count, the use of novel antibodies and need of only a small volume of blood (Practical-Haemostasis). For a quantitative analysis of epitopes expression, either blood sample stabilized *ex vivo* or diluted WB containing platelets previously stimulated *in vitro* is preferred (Schmitz *et al* 1998). Such activated platelets may be analyzed in WB with the use of activation-dependent monoclonal antibody by flow cytometry (Shattil *et al* 1987).

For all these reasons, in our clinical study, we aimed to compare the use of WB and PRP for detection of platelet activation by the use of flow cytometry and to reliably clarify the preference of the WB method to avoid any potential misinterpretations of results. To be clearer, we examined whether PRP preparation using a centrifugation step could result in platelet activation. The expression of the CD62P+ glycoprotein as one of the commonly used activation markers in platelet analysis was measured on CD42+ cells in our cohort of healthy donors.

Using the analysis of platelet activation in 50 healthy blood donors, we observed a higher proportion of CD62P+ events in PRP samples than in WB samples. This finding is even more pronounced when individual differences of individual donors were considered.

Due to the processing of the blood to prepare PRP, the co-expression of CD42a-FITC / CD62P-PE in PRP in healthy blood donors was increased in a statistically significant manner ($p< 0.0005$) when compared with WB (Table 1).

In our experiments, WB was centrifuged to make PRP and then resuspended back to WB sample. After this procedure, there was a persistence of the increase in the expression of CD62P in PRP. Therefore, we can confirm that the increase in CD62P staining was not due to the processing of the sample to prepare PRP.

Based on our results, we recommend to use non-processed, anticoagulant-treated WB as a standard method for studies of platelets and their activation status.

The limitation of our study is the fact that we could not exclude sodium citrate/hirudin-activated platelets in citrated PRP. Additionally, we might not detect microparticle populations due to technical reasons (detection limit of the analyzer used in the study is 0.5 µm, so the gating is also the problem when using smaller sizes).

We would now like to focus our further research to investigate these parameters, which were not assessed in the current study. In the future, we would like to detect and monitor the presence of the activation features of microparticles. Moreover, we would like to generalize this study design to a broader patient population.

Acknowledgements

This work was supported by the Agency for the support of Research and Development (APVV); under Grant APVV-16-0020; Scientific Grant Agency (Vega) under Grant Vega 1/0168/16 and Grant Vega 1/0549/19.

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Journal-based CPD No. 72
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Questions relating to the article *'Analysis of cerebrospinal fluid for xanthochromia in the investigation of subarachnoid haemorrhage: experience of a state-wide, tertiary referral trauma centre'* at page 121 of this issue.

1.	Subarachnoid haemorrhage (SAH) is spontaneous arterial bleeding into the subarachnoid space, which is associated with high mortality and morbidity.	True/False
2.	Seventy-eight CSF samples were received for xanthochromia testing; 2018–2019.	True/False
3.	It is estimated that up to 30 % of patients die immediately without any warning symptoms (Perry *et al* 2011).	True/False
4.	Evidence suggests that there is close to 100 % sensitivity for a negative Non Contrast-Computed Tomography of the Brain (NC-CTB) when performed within 8 hours of symptom onset.	True/False
5.	Early diagnosis and treatment are critical in reducing the otherwise high morbidity and mortality associated with SAH.	True/False
6.	Given the low prevalence of SAH, it is suggested that 0.4% of LPs will be positive (Sayer *et al* 2015).	True/False
7.	The presence of xanthochromia in CSF was determined by spectrophotometry.	True/False
8.	Over the period studied, 78 CSF samples (1 sample per patient) were received for the detection of xanthochromia with 95% of samples from the RHH and of these, 90% from the Emergency Department.	True/False
9.	The median (range) time from onset of symptoms to presentation at a hospital was 12 (1–672) hours.	True/False
10.	Other investigators have also reported a significant number (36 %) of inappropriate CSF xanthochromia requests (Goyale *et al* 2016).	True/False

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Journal-based CPD No. 73
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Questions relating to the article *'Comparative analysis of platelet glycoprotein expression'* at page 131 of this issue.

1.	Platelet surface glycoproteins CD42a and CD62P are indicators of processes leading to platelet activation and aggregation.	True/False
2.	We compare the results of CD42a and CD62P expression detected by flow cytometric analysis between samples of whole blood (WB) and platelet-rich plasma (PRP) of 50 Caucasian healthy blood donors.	True/False
3.	The reliability of platelet function testing can not be improved by processing of WB.	True/False
4.	Receptors used to initiate activation and/or stimulation of mediators of hemostasis are also present on the platelet membrane.	True/False
5.	CD42a (glycoprotein (GP) IX) is a 22-kDa transmembrane protein associated with CD42b, CD42c and CD42d to form the GP Ib-V-IX complex.	True/False
6.	P-selectin (CD62P) acts as one of the cell adhesion molecules on the surface of activated platelets.	True/False
7.	Two major gating strategies for platelet analysis were traditionally used.	True/False
8.	We chose quadrant statistical analysis of events gated in the platelet region in the forward scatter/ side scatter (FSC/SSC) dot plot.	True/False
9.	Several studies that detected platelet activation markers with the use of flow cytometry on the samples of PRP have been performed.	True/False
10.	It is suggested that the preparation of PRP provokes premature platelet activation (Augustine *et al* 2016).	True/False

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Please photocopy this page or print it from the electronic AJMS which is stored in the AIMS 'Member Centre' under the heading 'Journal' at www.aims.org.au. Circle your answers then scan and email to us:

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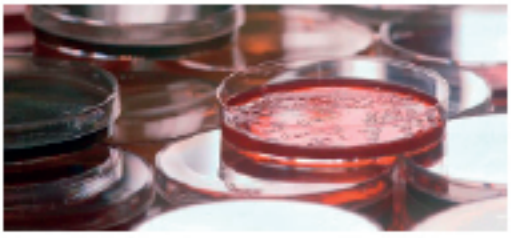

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1. **Bifidobacteria: Genomics & Molecular Aspects** edited by B. Mayo, & D. Van Sinderen. Caister Academic Press. xii + 260 pages.

2. **Medicine and Sport Science Volume 55: Cytokines, Growth Mediators & Physical Activity in Children during Puberty** edited by J. Jurimae, A.P. Hills & T. Jurimae. Karger. viii+178 pages.

3. **Digestive Diseases The Keys to IBD 2010: Treatment, Diagnosis & Pathophysiology.** Edited by G. Rogler & W. Sandborn. Karger. 188 pages.

4. **Else Kröner-Fresenuis Symposia Volume 1: Molecular Mechanisms of Adult Stem Cell Aging** edited by K.L. Rudolph. Karger. xii+108 pages**.**

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8. **Generic: The Unbranding of Modern Medicine** by Jeremy A. Greene. John Hopkins University Press. 368 pages.

9. **Human Pathogenic Fungi: Molecular Biology and Pathogenic Mechanisms** edited by Derek J. Sullivan & Gary P. Moran, Caister Academic Press. x + 342 pages.

10. **Internal Medicine: A Doctor's Stories** by Terrence Holt. Black Inc. 273 pages.

11. **Intolerant Bodies: A Short History of Autoimmunity** by Warwick Anderson and & Ian R. Mackay. John Hopkins University Press. 250 pages.

12. **More Than Hot: A Short History of Fever** by Christopher Hamlin. John Hopkins University Press. 400 pages.

13. **Pediatric and Adolescent Medicine Volume 19: Metabolic Syndrome and Obsesity in Childhood and Adolescence** edited by W. Kiess, M. Wabitsch, C. Maffeis, A.M. Sharma. Karger. x + 202 pages.

14. **Phage Therapy - Current Research and Applications** edited by Jan Borysowski, Ryszard Miedzybrodzki & Andrzej Gorski. Caister Academic Press. 368 pages.

15. **Shigella: Molecular and Cellular Biology** edited by William D. Picking & Wendy L. Picking. Caister Academic Press. 280 pages

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AUSTRALIAN JOURNAL OF MEDICAL SCIENCE

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The following instructions are based on the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", also known as the Declaration of Vancouver, and on the *Australian Government Style manual: for authors, editors and printers*, 6th edition, 2002. URLs were correct on September 29th, 2008.

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All individuals listed as authors must have made a substantial contribution to the conception and design of the study, the acquisition of data or the analysis and interpretation of data; the drafting of the article or revising it critically for important intellectual content; and final approval of the version to be published. The corresponding author must take responsibility for obtaining permission from all the authors for the submission of any version of the manuscript and for any changes in authorship.

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The abstract should be approximately 150 words and should make sense when read alone or in conjunction with the article. The abstract should be a concise overview that describes the important details of the article including the purpose of the study/investigation, basic procedures (study subjects/experimental animals/observational and analytic methods) and the results and principal conclusions. New and important aspects of the work and its implications may also be included. References should not be included.

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- Results
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- References

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Clearly state the purpose of the article leading the reader from the known to the unknown. Summarise the rationale for the study and state the question to be answered as appropriate. Give only strictly pertinent references, and do not review the subject extensively.

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Acknowledgements

Acknowledge individuals who have made substantial contributions to the study including technical work and financial support. Authors are responsible for obtaining consent from all the individuals acknowledged by name as inclusion may be interpreted as an endorsement of the article's contents.

References

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Personal Author(s) of a book:

Osler AG 1976. *Complement: mechanisms and functions*. Englewood Cliffs: Prentice-Hall.

Editor, Compiler, Chairman as Author:

Rhodes AJ, Van Rooyen CE, comps. 1968. *Textbook of virology: for students and practitioners of medicine and the other health sciences*. 5th ed. Baltimore: Williams and Wilkins.

Chapter in Book:

Weinstein L, Swartz MM 1974. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: WB Saunders; 457-472.

Online documents:

National Center for Biotechnology Information. OMIM: online Mendelian inheritance in man. http://www.ncbi.nlm.nih.gov/omim. Accessed February 25, 2007.

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In preparing tables, consideration should be given to the page width of the Australian Journal of Medical Science. All tables should be prepared for publication vertically. In the text, cite each table in consecutive order, and mark in the margin of the text its approximate location.

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Use only standard abbreviations (see list of commonly used abbreviations).

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Commonly used abbreviations

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g	gravity
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h	hour
IU	international unit
K	kelvin
kg	kilogram
L	liter, litre
m	meter, metre
min	min
M	molar
mL	millilitre
mol	mole
N	newton
nm	nanometre
p	probability
rpm	revolutions per min
s	second
wk	week
yr	year

Additional information

The following are useful sources of information. The first two publications are used by the AJMS as standard references.

Style Manual Committee. Council of Biology Editors. *Scientific style and format: the CBE manual for authors, editors, and publishers.* 6th ed. Cambridge University Press, 1994.

Style manual for authors, editors and printers. 6th ed. John Wiley & Sons Australia Ltd, 2002.

O'Connor M, Woodford FP. *Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors.* Amsterdam, Oxford, New York: Elsevier-Excerpta Medica, 1975.

Day RA. *How to write and publish a scientific paper.* Philadelphia, Institute for Scientific Information Press, 1979.

Zeiger M. *Essentials of writing biomedical research papers*. 2nd ed. New York, McGraw-Hill, 2000.

Matthews JR, Matthews RW. *Successful scientific writing: a step-by-step guide for the biological and medical sciences*. 3rd ed. Cambridge, Cambridge University Press, 2007 [Also available in eBook format.]

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